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Heart Disease Case Finding by Means of 70 Millimeter Photofluorographic Films

Group I

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These studies concern the value of the 70 mm. photofluorographic tuberculosis film as a heart disease case finding procedure. The yield of cases discovered and benefited in the group I study would be considered satisfactory in comparison with yields usually obtained in mass surveys for other diseases. This was not so in the group II study, and the reasons for the differences are discussed.

MANY communities, in conducting mass chest x-ray surveys with 70 mm. photofluorographic films for tuberculosis case finding, have been faced with the question of the usefulness of such films in heart disease case finding. It has long been recognized that the posterior-anterior chest film is not an ideal heart disease case finding procedure because some patients with heart disease have normal cardiac silhouettes in this projection. It is therefore impossible to use this method for the determination of the incidence or prevalence of heart disease. The practical question, however, still remains: Is it possible, by means of the 70 mm. photofluorographic film, as taken for tuberculosis, to identify in the general population a significant number of individuals with previously unknown heart disease who will be benefited by such identification?

There have been reported a number of investigations making use of mass x-ray technic for heart disease case finding in special population groups, but no such study has been reported which deals with a general population group and in which a uniform procedure for re-examination has been utilized for those whose films appear suggestive of heart disease.

Robins and Ehrlich[1] reported in 1940 that in x-ray surveys in New York City they found abnormal cardiac silhouettes in the indicated percentages in the following special population groups: high school students, 0.7 per cent; home relief population, 2.4 per cent; prisoners, 7.6 per cent; homeless men, 3.9 per cent. There is no report of follow-up on these films.

In the same year, Green[2] reported on a survey of a relief population, 70 per cent Negro, in

From the Committee on Cardiac Case Finding of the Massachusetts Heart Association (Dr. Benedict F. Massell, Chairman, Dr. C. Sidney Burwell, Dr. Laurence B. Ellis, Dr. Merrill C. Sosman and Dr. David D. Rutstein). This type of study requires the cooperation of many individuals representing many disciplines, and in this report the authors act as spokesmen for all those whose cooperation is acknowledged. They do, however, accept full responsibility for the analysis and interpretation of the data in this paper.

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the Harlem area of New York City from December, 1936 to December, 1938. Of a total of 22,219 films, 1652 or 7.4 per cent showed abnormal cardiac silhouettes. Of the 1652 persons with abnormal films, 1008 or 61 per cent reported for examination. Of these 1008 persons, 814 or 80.8 per cent were found to have heart disease. Of these 814 cases, 564 or 69.3 per cent were previously unaware of their heart disease. Thus in this special population group of 22,219, 564 individuals (2.5 per cent) with previously unknown heart disease were identified.

Thompson and Jellen,[3] in a paper evaluating heart size in four by five inch films, reported incidentally that of 1147 persons having abnormal cardiac silhouettes and reviewed clinically, 68.9 per cent had heart disease confirmed, and that among those with heart disease, 62.2 per cent had no previous knowledge of its existence. These results are difficult to evaluate, because the industrial population group under survey was not defined.

In a Glasgow survey, Maclean and Rogen[4] reported in 1949 that among 34,918 relatively young persons (two-thirds under age 20) studied by mass x-ray and questioned as to history of rheumatic fever or rheumatic heart disease, only 21 cases of rheumatic heart disease and two cases of congenital heart disease were found which were previously unknown.

The practical question raised above is not answered by published studies, and in an attempt to bring additional data to bear on this question, a study was conducted in connection with the Boston Chest X-ray Survey of 1949–50. Two separate groups of chest films, selected in different ways, were drawn from the total survey for study. The results of these two studies are so strikingly different that it has been felt desirable to publish the results in two separate papers simultaneously in the same journal, followed by a third paper in which the practical applications of the survey results are discussed. The results reported in this paper are those obtained from the study of group I.

Method

The Health Foundation of Boston, Inc., composed of official and nonofficial agencies,* in cooperation with the United States Public Health Service, conducted a chest x-ray survey primarily for tuberculosis case finding in Boston from September 21, 1949 to January 14, 1950. In the course of the survey, approximately 536,000 70 mm. photofluorographic films were taken at a focal-film distance of 40 inches, the procedure usual in mass chest x-ray surveys. The films were read, in accordance with practice in other similar surveys, by Public Health Service medical officers (hereafter called "regular" readers) for suspected tuberculosis, other chest disease, and abnormalities of the silhouette of the heart and great vessels.

For the purpose of this study, a selection was made of 81 rolls of film (Group I) from the 818 survey rolls read by regular readers during the latter part of the survey (November 10, 1949 to January 25, 1950). The Group I rolls included films for 31,091 persons, exclusive of approximately 750 films which were classified abnormal for diseases other than heart disease. These 81 rolls of film were then submitted for re-reading to a special group of radiologists (hereafter designated as "special" readers), who worked in pairs.

Each film in Group I, therefore, was subjected to two independent readings—the first by the regular readers in the manner usual to the mass chest x-ray survey, where the primary interest is the finding of tuberculosis, and the second by the special readers, who were solely interested in finding abnormalities in the size and shape of the silhouette of the heart and great vessels. Both groups of readers read the films by observation and not by measurement. Films showing enlargement or distortion of the silhouette of the heart or great vessels were classified as abnormal.

All persons whose cardiac shadows were classified as abnormal by either or both groups of readers were requested by letter to make an appointment for examination at a special clinic established at the Peter Bent Brigham Hospital under the direction of one of the authors (C. R. W.). Follow-up of nonrespondents was made by telephone, mail, home visits by visiting nurses of the Boston Visiting Nurse Association, and through the persons' physicians where known.

The special clinic, held evenings and Saturday afternoons, was staffed by competent cardiologists. Each person received an initial examination consisting of a history, including that of knowledge of preexisting heart disease, physical examination and electrocardiogram. If definite clinically significant heart disease was disclosed by any one or combination of these procedures, no additional examinations were performed. When no definite diagnosis of heart disease could be made by these procedures, a fluoro-

* Including Boston Health Department, Massachusetts Department of Public Health, Massachusetts Medical Society, Boston Tuberculosis Association, Massachusetts Tuberculosis and Health League, and New England Heart Association (now the Massachusetts Heart Association).

scopic examination was performed, and when necessary, further x-rays were taken. Thus a diagnosis of "no heart disease" or of "borderline heart disease" was never made without a complete work-up consisting of a history, physical examination, electrocardiogram and fluoroscopic and radiologic examination. History and physical findings were recorded on a form specially prepared for this study. These forms were reviewed at the conclusion of the study by two of the authors (D. D. R. and C. R. W.) and each case classified as "verified heart disease," "borderline heart disease," or "negative."

A report of the findings of each examination was sent to the physician of each person examined. No medical information was sent to the person himself; he was informed either that he had no heart disease or that he should report to his physician.

Population Studied

The base population for this study was a group of persons who presented themselves voluntarily for filming in a mass tuberculosis survey. A lower age limit of 16 had been set, but there were a few persons under that age; there was no upper age limit. In general, as shown in table 1, the 31,091 persons in group I did not vary markedly in age-sex distribution from the population 15 and over in the Boston Metropolitan District.* There was a slight excess of males in group I, and specifically an excess of males 15 to 29. Group I was low for both males and females at ages 50 to 59, and low for females 60 and over. None of these differences has any significant effect on the conclusions reported in this paper. They reflect a situation usually found in chest x-ray surveys, namely, an under-representation of persons in the older age groups.

Findings

Clinically Positive Cases

Yield. Among the 31,091 films read by the two groups of readers, 1,101 films (3.54 per cent) were classified as abnormal (table 2). Among the 1,101 individuals whose films were classified as abnormal, 845 (76.7 per cent) returned for examination.† This group comprises 2.72 per cent of the base population of 31,091. Among the 845 individuals examined, 504 (1.62 per cent of the base population) were found to have clinically significant heart disease.‡ Among the 504 in whom clinical heart disease was verified, 280 had no knowledge of the existence of heart disease at the time the survey films were taken. This last group comprises 0.90 per cent of the base population.

TABLE 1.—*Comparison of Age and Sex Distribution, Boston Metropolitan District, 1947, and Survey Population, 1949–50.*

Group I

	Boston Metro. District 1947*		Survey Population, 1949–50	
	Male	Female	Male	Female
Population	911,325	1,046,025	15,255	15,836
Per cent distribution				
All ages	46.6	53.4	49.1	50.9
15–29	13.7	15.5	18.9	15.3
30–49	17.9	20.5	18.8	21.7
50–59	9.8	10.4	6.2	8.2
60 and over	5.2	7.0	5.2	5.7

* Adapted from Bureau of the Census Sample Survey, April, 1947.

TABLE 2.—*Yield of Abnormal Films and Cases of Verified Heart Disease*

Group I

	Number	Per cent
Survey population	31,091	100
Abnormal films	1,101	3.54
Cases examined	845	2.72
Cases verified heart disease	504	1.62
Cases previously unknown	280	0.90

Age. Table 3 indicates that the older the individual, the greater the likelihood of his having an abnormal film. This is an expected result since the occurrence of heart disease in-

* The survey, while operating film units only in the city of Boston, drew persons from all over the greater Boston area. The base population data most nearly comparable are the estimates based on a Bureau of the Census survey of the Boston Metropolitan District as of April, 1947.

† There was a possibility that a selective factor might have been introduced because not all of those whose films were read as abnormal returned for examination. The data in this paper have been analyzed for this factor, and it does not significantly affect the conclusions in this paper. (See discussion on Findings—Nonrespondent Group.)

‡ In addition, there were 57 individuals whose heart disease was classified as borderline, and these are described briefly under Borderline Cases.

creases with age Thus the rate at which the films were classified as abnormal rose from 1.85 per cent in the 15 to 29 year age group to 10.75 per cent in the age group of 60 and over, the over-all percentage of the base population being 3.54 per cent.

Among the 845 individuals who returned for examination, there were 504 or 59.6 per cent who were found to have clinically significant heart disease (table 2). It is clinically significant, as indicated in table 3, that the precision of film reading increases with the age of the subject. Thus, the rate at which heart disease was verified among those with abnormal films returning for examination rose from 20.4 per cent in the 15 to 29 year age group to 82.0 per cent in the age group of 60 and over. It is particularly striking that only one out of five examined individuals suspected of having heart disease on the original films in the age group 15 to 29 had clinically significant heart disease on examination. This result is probably in part dependent on the relative difficulty in interpretation of changes in the left border of the cardiac silhouette, so important in the diagnosis of heart disease in young people. However, the increasing precision at advanced ages is not so significant as it might appear, since even if no films were taken, the probability of finding heart disease among any random group of older people is greater. This latter effect is impossible to estimate accurately, but it is hardly likely that it would invalidate the conclusion that the older the individual x-rayed, the more precise will be the reading of the film.

There were 280 (55.6 per cent) of the 504 individuals (table 2) with clinically significant heart disease who gave no history of knowledge of the existence of heart disease. Age significantly affected this result. Among those with clinically significant heart disease, a larger proportion of persons in the age group 50 and over were unaware of their disease than was the case in the age group 15 to 49 (59.9 per cent as compared with 44.9 per cent). Thus the yield of previously unknown cases of clinically significant heart disease in the younger age groups was further reduced by this effect.

Sex. Sex was a significant factor, since the rates for females were double those for males in every category studied (table 4): films classified abnormal (4.68 per cent of females compared with 2.35 per cent of males); heart disease verified (2.14 per cent compared with 1.08 per cent), and heart disease verified previously unknown (1.21 per cent compared with 0.58 per cent). It might appear that this result was associated with the longer life expectancy of females. However, examination of detailed data by age and sex (Appendix table 1) showed that this was not the case, because the same ratio appeared in the younger as well as the older age group.

Race. Race was a significant factor since the rates for nonwhites were double those for whites in every category studied (table 4): films classified abnormal (6.33 per cent of nonwhites compared with 3.36 per cent of whites); heart disease verified (2.95 per cent compared with 1.54 per cent) and heart disease verified previ-

TABLE 3.—*Yield of Abnormal Films, Cases of Verified Heart Disease, and Previously Unknown Heart Disease, by Age*

Group I

	Survey population	Per cent of survey population with:			Abnormal film cases examined	Per cent of examined population with:	
		Abnormal films	Verified heart disease	Heart disease previously unknown		Verified heart disease	Heart disease previously unknown
All ages	**31,091**	**3.54**	**1.62**	**0.90**	**845**	**59.6**	**33.1**
15–29	10,634	1.85	0.31	0.12	162	20.4	8.0
30–49	12,584	2.12	0.91	0.42	223	51.1	23.8
50–59	4,487	6.08	3.30	2.18	205	72.2	47.8
60 and over	3,386	10.75	6.17	3.42	255	82.0	45.5

ously unknown (1.50 per cent compared with 0.86 per cent). It is of interest to note that among those with verified heart disease, previous knowledge of its existence was about the same in both the white and nonwhite groups.

When these data were studied by race and sex (table 4), the differences already noted were compounded, so that the rates in every category studied were about four times as great for nonwhite females as they were for white males: films classified abnormal (9.45 per cent compared with 2.24 per cent); heart disease verified (4.17 per cent compared with 1.01 per cent); and heart disease verified previously unknown (1.96 per cent compared with 0.53 per cent). As might have been expected, where these significant factors operated singly, that is, sex in white females and race in nonwhite males, the rates for these were about the same (table 4). These data would further indicate that the greatest yields in heart disease surveys can be obtained in nonwhite populations and among females. This excess of heart disease among nonwhites is a result in this group of an excess of cases of hypertensive and arteriosclerotic heart disease among older individuals, and is not due to heart disease caused by syphilis.

TABLE 4.—*Yield of Abnormal Films, Cases of Verified Heart Disease, and Cases of Heart Disease Previously Unknown, by Race and Sex*

Group I

	Survey population	Per cent of survey population with:			Abnormal film cases examined	Per cent of examined population with:	
		Abnormal films	Verified heart disease	Heart disease previously unknown		Verified heart disease	Heart disease previously unknown
Total, survey population	**31,091**	**3.54**	**1.62**	**0.90**	**845**	**59.6**	**33.1**
Male	15,255	2.35	1.08	0.58	266	62.0	33.1
Female	15,836	4.68	2.14	1.21	579	58.5	33.2
White	**29,227**	**3.36**	**1.54**	**0.86**	**755**	**59.5**	**33.4**
Male	14,206	2.24	1.01	0.53	237	60.8	32.1
Female	15,021	4.43	2.03	1.17	518	58.9	34.0
Nonwhite	**1,864**	**6.33**	**2.95**	**1.50**	**90**	**61.1**	**31.1**
Male	1,049	3.91	2.00	1.14	29	72.4	41.4
Female	815	9.45	4.17	1.96	61	55.7	26.2

Etiology. Frequencies of the etiologic categories of the verified heart disease cases found in this survey (table 5) were those which might be expected from the age distribution. The most frequently occurring categories are hypertensive heart disease (38.7 per cent), hypertensive and arteriosclerotic heart disease (17.7 per cent), and rheumatic heart disease (16.9 per cent). When these 504 verified heart disease cases are studied from the point of view of any one etiologic category without regard to the simultaneous occurrence of other etiologic categories in the same individual (table 5), the major ones were hypertensive heart disease (64.7 per cent), arteriosclerotic heart disease (31.9 per cent) and rheumatic heart disease (26.6 per cent).

The classification of the 280 cases of heart disease verified previously unknown fell into a pattern similar to that of the total group of 504 verified cases, except that hypertensive heart disease occurred more frequently and rheumatic heart disease somewhat less frequently in this group (table 5). This was to be expected in the light of the greater awareness of the existence of heart disease among those with verified heart disease in the younger age groups.

Benefit. A successful survey must not only find cases of disease previously unknown, but knowledge and facilities must be available to benefit the discovered cases. "Benefit" is difficult to define, but in this study has been arbitrarily defined to include all cases with

heart disease previously unknown falling in the following categories:

(1) All cases of rheumatic heart disease. Benefits which might accrue to such patients through knowledge of the existence of their disease are the prevention of exposure to hemolytic streptococcal infection, prevention of subacute bacterial endocarditis after tooth extraction or operation, and vocational rehabilitation for younger patients.

(2) All cases not under medical care, having verified hypertensive or arteriosclerotic heart disease, who also had congestive failure, auricular fibrillation with heart rate greater than 100, angina pectoris, or marked obesity. It is to be noted that cases of hypertensive and arteriosclerotic heart disease who were under medical care, but who had congestive failure not receiving digitalis, auricular fibrillation with a rapid heart rate not receiving digitalis, angina pectoris not receiving nitroglycerin, or who had marked obesity, were not placed in the "benefited" group because there were no facilities for obtaining follow-up information on changes in treatment after a report of the survey examination was sent to the patient's physician.

(3) A miscellaneous group of cases, consisting of congenital heart disease which might be relieved by surgery or where subacute bacterial endocarditis might be prevented, syphilitic heart disease where specific therapy might be given, thyrotoxic heart disease which might be relieved by medical or surgical therapy, pericardial tumor possibly amenable to surgery, and a group of cases of unknown etiology, most of which were probably congenital, not under medical care and probably amenable to preventive or therapeutic measures.

TABLE 5.—*Etiologic Classification of Cases of Verified Heart Disease and Cases Previously Unknown.*

Group I

	Cases of verified heart diseases		Cases previously unknown	
	Number	Per cent	Number	Per cent
All etiologic classifications	**504**	**100**	**280**	**100**
Rheumatic	85	16.9	26	9.3
Hypertensive	195	38.7	150	53.6
Arteriosclerotic	47	9.3	20	7.1
Rheumatic and hypertensive	24	4.8	8	2.9
Rheumatic and arteriosclerotic	7	1.4	3	1.1
Hypertensive and arteriosclerotic	89	17.7	40	14.3
Rheumatic, hypertensive and arteriosclerotic	18	3.6	7	2.5
Other	15*	3.0	7	2.5
Unknown	24	4.8	19	6.8
Major etiologic classifications (with duplication):				
Rheumatic	**134**	**26.6**	**44**	**15.7**
Hypertensive	**326**	**64.7**	**205**	**73.2**
Arteriosclerotic	**161**	**31.9**	**70**	**25.0**

* "Other" verified heart disease cases include: six congenital, five syphilitic, one hyperthyroid, one pericardial, one pulmonary.

TABLE 6.—*Persons Benefited among Previously Unknown Cases of Verified Heart Disease**

Group I

Etiology and remediable condition	Number	Per cent
All cases benefited*	**128**	**100**
Rheumatic	26	20.3
Hypertensive	58	45.3
Obesity	54	
Congestive failure	4	
Arteriosclerotic	12	9.4
Obesity	3	
Congestive failure	2	
Angina pectoris	7	
Hypertensive and arteriosclerotic	14	10.9
Obesity	9	
Congestive failure	2	
Angina pectoris	2	
Other	1	
Other	18	14.1

* Does not include 18 persons who believed they had heart disease when the survey films were taken whose chest films were classified abnormal, but were found on complete examination to have normal hearts and who were therefore believed to have been benefited.

Of the 280 cases of verified heart disease previously unknown, there were 128 cases (45.7 per cent) who fitted into one of these categories (table 6). The 128 cases classified as benefited

comprised 0.41 per cent of the base population. In addition, this survey picked up cases, exact number not determined, of previously known heart disease who were not under regular supervision of their physicians at the time of the survey and who were benefited by return to medical supervision.

There was one other category of individuals who did not have verified heart disease but who have been benefited by this survey. This category includes the 18 individuals who believed they had heart disease at the time the survey film was taken, whose chest films were classified as abnormal, but who were found on complete examination to have normal hearts.

Readers. Table 7 (and Appendix table 2) indicate the difference in the reading of the original films by the regular and special readers. Of the 1,101 films classified abnormal, 108 (0.35 per cent of the surveyed population) were classified abnormal by the regular readers only. A much larger number, 756 or 2.43 per cent, were similarly classified by the special readers only; 237 films (0.76 per cent) were considered abnormal by both groups of readers.

When studied from the point of view of the total contribution of abnormal film readings made by each group of readers, it was found that the special readers who read the films only for heart disease contributed almost three times as many (993 or 3.19 per cent of films read) as the regular readers, who read the films rapidly for all chest abnormalities with primary emphasis on tuberculosis (345 or 1.11 per cent).

The special readers, although classifying approximately three times as many films as abnormal, read almost as precisely as the regular readers. Heart disease was verified in 61.0 per cent of the examined cases contributed by the reading of the special readers as compared with 69.6 per cent verification of the reading of the regular readers. As might be expected, the precision of reading was greatest in the group of films classified as abnormal by both groups: 81.1 per cent of those examined having verified heart disease.

TABLE 7.—*Yield of Abnormal Films, Cases of Verified Heart Disease, and Cases of Previously Unknown Heart Disease, by Reader Group*

Group I

	Films read (survey population)	Per cent of 31,091 films read with finding of:			Abnormal film cases examined	Per cent of examined cases with:	
		Abnormal films	Verified heart disease	Heart disease previously unknown		Verified heart disease	Heart disease previously unknown
All readers	**31,091**	**3.54**	**1.62**	**0.90**	**845**	**59.6**	**33.1**
Regular readers (total readings)		1.11	0.58	0.27	260	69.6	32.3
Special readers (total readings)		3.19	1.48	0.78	754	61.0	33.6
Regular readers only		0.35	0.14	0.09	91	48.4	29.7
Both regular and special readers		0.76	0.44	0.18	169	81.1	33.7
Special readers only		2.43	1.04	0.63	585	55.2	33.5

Borderline Cases

In addition to the 504 identified cases with clinically significant heart disease among the 845 examined individuals, there were 57 other individuals in whom it was not possible to determine whether or not heart disease existed, and who were classified as "borderline cases." This group of 57 individuals differed from the positive group of cases in that most of them (48 out of 57) did not suspect the existence of heart disease at the time of the examination, and the female preponderance was even greater, that is, almost 3 to 1 as compared with 2 to 1. The borderline cases were identified because of suspicious findings in any one or combination of

the following examinations: fluoroscopy, 35; abnormal heart sounds or murmurs, 29; electrocardiography, 20; elevated blood pressure, 19; miscellaneous findings, eight. The exclusion of the borderline cases in calculating the yield of this study tends to minimize further the estimate of the yield since it is probable that some of the borderline cases did have heart disease.

TABLE 8.—*Probable Heart Disease Status of Nonrespondent Population*

Group I

	Number	Per cent
Nonrespondents—total	**256**	**100**
Probably Heart Disease	**62**	**24.2**
Cardiologist's report	30	11.7
Other physician's report	27	10.5
Dead, heart disease reported cause	5	2.0
Probably Not Heart Disease	**21**	**8.2**
Cardiologist's report	2	0.8
Other physician's report	19	7.4
Status Unknown or Uncertain	**173**	**67.6**
Other physician's report doubtful	2	0.8
Person reported heart disease (unverified)	20	7.8
Person reported no heart disease	19	7.4
Person contacted—no information	78	30.5
Not found	41	16.0
Reported out of area	12	4.7
Dead, cause not heart disease	1	0.4

Nonrespondent Group

After every effort had been made to secure a clinical examination on each of the 1,101 persons with a positive film reading, there remained 256 (23.3 per cent) who for a number of reasons did not come to the clinic for examination. At the conclusion of the clinical study, a final attempt was made to obtain information regarding the nonrespondent group by means of a letter to the individual and to his doctor. In this letter the individual or his doctor was requested to answer a series of questions indicating whether or not the person had heart disease.

Table 8 summarizes the information which was secured on the nonrespondent group. Approximately one fourth, 62 out of the 256, were reported by cardiologists or other physicians to have heart disease, or had died before the conclusion of the study with heart disease as the reported cause. Only 21 were reported by their physicians as not having heart disease. The remaining two-thirds of the 256 cases have been classified as status unknown or uncertain, although they included 20 persons who reported that they had heart disease, but for whom no report from a medical source could be secured. This information suggests, but does not prove, that there may have been as much heart disease in the nonrespondent as in the respondent group.

In order to make the most conservative estimate of the total yield of the survey, reported percentages have been based in the main on the total number of films read rather than on the number of individuals who returned for examination. This is equivalent to the assumption that no heart disease existed among the group of individuals who did not return for examination—which is contrary to the facts noted above. In taking this line of analysis, however, recognition is given to the practical difficulties in mass surveys in securing the return for examination of persons whose films are classified as abnormal.

LEVEL OF READING

The "level of reading," that is, the proportion of films classified by the readers as abnormal, has been discussed in previous sections of this paper and will be discussed in further detail in the second paper of this series, where the results of the second study group are reported.[5] There is, however, some internal evidence from the data collected in the total study that the level of reading of the regular readers for the films included in Group I was influenced by the knowledge that a cardiac study was being conducted. The apparent result was that the level of suspicion for cardiac abnormality was raised. However, it should be noted that in the analysis of Group I in this paper, attention was focused almost entirely on the combined readings of positive film cases reported by both regular and special readers, and this yield is considerably in excess of that found in the

usual course of reading in chest x-ray surveys. Since the increase in the number of films read positive by the regular readers is relatively small in comparison with those read positive by the special readers it would not appear that the increased level of reading in this paper by regular readers would materially affect the findings with respect to total yield.

TABLE 9.—*Summary of Heart Disease Case Findings by Chest X-Ray Survey*
Group I

	Number	Per cent of:				
		Survey population	Abnormal films	Cases examined	Cases verified	Cases previously unknown
Survey population	**31,091**	**100**				
Abnormal films	1,101	3.54	100			
Cases examined	845	2.72	76.7	100		
Cases verified heart disease	504	1.62	45.8	59.6	100	
Cases previously unknown	280	0.90	25.4	33.1	55.6	100
Benefited cases	128	0.41	11.6	15.1	25.4	45.7

SUMMARY AND CONCLUSIONS

1. A group of 31,091 70 mm. photofluorographic films taken for tuberculosis in the Boston Chest X-ray Survey were read for the existence of an abnormal cardiac silhouette by two groups of readers: (a) U. S. Public Health Service Medical Officers, who read the films for all abnormalities, and (b) radiologists from Boston hospitals, working in pairs, who read the films only for abnormalities of the silhouette of the heart and great vessels.

2. The base population of the study was distributed as to age and sex in about the same manner as the population of Greater Boston, but with a slight excess of males, and some under-representation of age groups over 50.

3. Of the 31,091 films, 1,101 or 3.54 per cent were classified as abnormal.

4. Of the 1,101 individuals whose films were classified abnormal, 845 or 76.7 per cent returned for examination. This group of 845 represents 2.72 per cent of the base population.

5. Of the 845 individuals examined, heart disease was verified in 504, or 59.6 per cent. This group of 504 represents 1.62 per cent of the base population and 45.8 per cent of those individuals whose films were classified as abnormal.

6. Of the 504 individuals in whom heart disease was verified, 280 or 55.6 per cent had no previous knowledge of its existence. This group represents 0.90 per cent of the base population, 25.4 per cent of those whose films were classified as abnormal, and 33.1 per cent of all persons examined.

7. Of the 280 individuals in whom heart disease was verified but was previously unknown, 128 or 45.7 per cent were "benefited." This group represents 0.41 per cent of the base population, 11.6 per cent of those whose films were classified as abnormal, 15.1 per cent of all persons examined, and 25.4 per cent of those with clinically significant heart disease.

8. Abnormal films, verifiable heart disease, and verifiable heart disease previously unknown increased with advancing age.

9. A clinically significant finding was the increase in precision of film reading with advancing age of the subject, the precision increasing from 20.4 per cent in the age group 15 to 29 to 82.0 per cent in the age group 60 and over.

10. Among females, who appeared in the base population at the same frequency as males, abnormal films, verifiable heart disease, and verifiable heart disease previously unknown occurred twice as frequently as among males.

11. Among nonwhites, abnormal films, verifiable heart disease, and verifiable heart disease previously unknown occurred twice as frequently as among whites.

12. Most of the cases of verified heart disease

APPENDIX TABLE 1.—*Survey Population, Abnormal Films, Cases Examined, Cases of Verified Heart Disease, Verified Cases Previously Unknown, and Benefited Cases, by Sex, Age and Sex, and Race and Sex.*

Group I

	Survey population	Yield of:				
		Abnormal films	Cases examined	Cases of verified heart disease	Verified cases previously unknown	Benefited cases
Total	**31,091**	**1,101**	**854**	**504**	**280**	**128**
Male	15,255	359	266	165	88	46
Female	15,836	742	579	339	192	82
By age and sex:						
15–29	**10,634**	**197**	**162**	**33**	**13**	**11**
M	5,884	74	60	12	5	3
F	4,750	123	102	21	8	8
30–49	**12,584**	**267**	**223**	**114**	**53**	**28**
M	5,805	77	62	40	16	9
F	6,779	190	161	74	37	19
50–59	**4,487**	**273**	**205**	**148**	**98**	**51**
M	1,943	77	54	37	27	16
F	2,544	196	151	111	71	35
60 and over	*3,386*	*364*	*255*	*209*	*116*	*38*
M	1,623	131	90	76	40	18
F	1,763	233	165	133	76	20
By race and sex:						
White	**29,227**	**983**	**755**	**449**	**252**	**116**
M	14,206	318	237	144	76	41
F	15,021	665	518	305	176	75
Nonwhite	**1,864**	**118**	**90**	**55**	**28**	**12**
M	1,049	41	29	21	12	5
F	815	77	61	34	16	7

APPENDIX TABLE 2.—*Survey Population, Abnormal Films, Cases Examined, Cases of Verified Heart Disease, Verified Cases Previously Unknown, and Benefited Cases, by Reader Group*

Group I

	Films read (survey population)	Yield of:				
		Abnormal films	Cases examined	Cases of verified heart disease	Verified cases previously unknown	Benefited cases
All readers	**31,091**	**1,101**	**845**	**504**	**280**	**128**
Total contribution by:						
Regular readers	*	345	260	181	84	30
Special readers	*	993	754	460	253	114
Separate contribution by:						
Regular readers only	*	108	91	44	27	14
Both regular and special readers	*	237	169	137	57	16
Special readers only	*	756	585	323	196	98

* All 31,091 films were read by representatives of each group of readers.

previously unknown were classified into the etiologic categories of hypertensive, combined hypertensive and arteriosclerotic, and rheumatic, in that order.

13. "Special" readers classified films as abnormal at three times the rate of the "regular" readers, but with almost the same degree of precision.

14. In addition to the clinically positive cases, there was a total of 57 "borderline cases." The characteristics of this group are discussed.

15. The nonrespondent group is known to contain a large number of verified or verifiable heart disease cases. Since these are not included, estimates based on the total population tend to understate the actual yield of this study.

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Heart Disease Case Finding by Means of 70 Millimeter Photofluorographic Films

Group II

By CHARLES R. WILLIAMSON, M.D., FELIX E. MOORE, AND DAVID D. RUTSTEIN, M.D.

THE first paper in this series[1] presented the results of heart disease case finding in the Boston Chest X-Ray Survey for tuberculosis, utilizing 70 mm. photofluorographic films which were read by the survey team for all abnormalities and then reread by a special group of radiologists, working in pairs, solely for abnormalities of the size and shape of the cardiac silhouette. This is a report of heart disease case finding on another group of films in the same x-ray survey where the conditions were those usual to most mass chest x-ray surveys, that is, where all the films are read once by a survey team for all possible chest abnormalities including those of the heart and great vessels. The results so obtained are so different from those of the previous paper that they are reported separately.

METHOD

Group II, on which this study is based, includes 99,791 films (from the total of about 536,000 films taken in the 1949–50 Boston Chest X-Ray Survey) read between December 8, 1949 and January 12, 1950. The rolls in this group were read as units by the United States Public Health Service medical officers. Persons classified as having abnormalities in the size and shape of the silhouette of the heart and great vessels were handled in exactly the same manner as those in group I as regards clinical examination, cardiac classification, reporting of findings to private physicians and follow-up of the nonrespondents.

Comparison of the base population data of this survey group with the population estimates for the Boston Metropolitan District (based upon a Bureau of the Census survey carried out in April, 1947) shows that there is some under-representation in this group of the age groups 50 and over (table 1). In general, however, it will be seen that the age and sex distribution in the survey group approximates very well that of the Greater Boston area, and the minor differences have no significant effect on the conclusions reported in this paper.

FINDINGS

Clinically Positive Cases

Yield. Among the 99,791 films read, 410 films (0.41 per cent) were classified as abnormal (table 2). Among the 410 individuals whose films were classified abnormal, 309 (75.4 per cent) returned for examination.* This group comprises 0.31 per cent of the base population of 99,791. Among the 309 persons examined, 233 (0.23 per cent of the base population) were found to have clinically significant heart disease.† Among the 233 in whom clinical heart disease was verified, 74 had no knowledge of

From the Committee on Cardiac Case Finding of the Massachusetts Heart Association (Dr. Benedict F. Massell, Chairman, Dr. C. Sidney Burwell, Dr. Laurence B. Ellis, Dr. Merrill C. Sosman and Dr. David D. Rutstein). This type of study requires the cooperation of many individuals representing many disciplines, and in this report the authors act as spokesmen for all those whose cooperation is acknowledged. They do, however, accept full responsibility for the analysis and interpretation of the data in this paper.

This study was supported equally by grants from the Massachusetts Heart Association and the U. S. Public Health Service.

Acknowledgment is made to the Subcommittee on Case Finding of the Joint Committee of the National Tuberculosis Association and the American Heart Association, who provided the initial impetus to the organization of the study.

* There was a possibility that a selective factor might have been introduced because not all those whose films were read as abnormal returned for examination. The data in this paper have been analyzed for this factor, and it does not significantly affect the conclusions in this paper. (See discussion on Findings —Nonrespondent Group.)

† In addition, there were 15 individuals whose heart disease was classified as borderline, and these are described briefly under Borderline Cases.

the existence of heart disease at the time the survey films were taken. This last group comprises 0.07 per cent of the base population. It is evident that the yield in this study was far below that reported in the previous study (group I), in which the yield of previously unknown heart disease was 0.90 per cent.[1]

Age. As in the previous study,[1] the older the individual the greater the likelihood of his having an abnormal film (table 3). Thus, the rate at which the films were classified as abnormal rose from 0.21 per cent in the 15 to 29 year age group to 1.39 per cent in the age group 60 and over, the over-all percentage of the base population being 0.41 per cent.

Among the 309 individuals who returned for examination, there were 233 or 75.4 per cent who were found to have clinically significant heart disease (table 3). In this study, as in the previous one, the precision of film reading increases with the age of the subject. Thus the rate at which heart disease was verified among those with abnormal films returning for examination rose from 38.3 per cent in the 15 to 29 year age group to 90.0 per cent in the age group of 60 and over. These percentages are higher for group II than for group I.[1] This might be explained by the relatively small yield in group II, which would suggest that only those films with striking changes in the silhouette of the heart and great vessels were read as abnormal in this study.

Table 3 also reveals a surprisingly low yield of cases with verified heart disease previously unknown in the younger ages. Actually, in the base population of 99,791, only two individuals between the ages of 15 and 29 were so identified, and only eight of such cases were discovered in the age group 30 to 49 (Appendix table 1). Among the 309 persons examined of all ages, there were 74 or 23.9 per cent in whom heart disease was verified and was previously unknown. This is but 0.07 per cent of the base population of 99,791 (table 3).

Sex. Sex was a significant factor, since the rates for females were about one and a half times those for males in every category studied (table 4): films classified abnormal (0.48 per cent of females compared with 0.34 per cent of males); heart disease verified (0.29 per cent compared with 0.18 per cent), and heart disease verified previously unknown (0.08 per cent compared with 0.06 per cent). This preponderance of females was not so great as in group I,[1] where there were about twice as many females as males in every category studied.

Race. Race was a significant factor, since the rates for nonwhites were at least two times those for whites in the studied categories (table 4): films classified abnormal (0.84 per cent of nonwhites compared with 0.39 per cent of whites); heart disease verified (0.59 per cent compared with 0.22 per cent), and heart disease verified previously unknown (0.31 per cent compared with 0.07 per cent). This significant preponderance of nonwhites over whites seemed somewhat greater than in group I, where the rates for nonwhites were just double those for whites.

TABLE 1.—*Comparison of Age and Sex Distribution, Boston Metropolitan District, 1947, and Survey Population, 1949–50*

Group II

	Boston Metro. District 1947*		Survey Population 1949–50	
	Male	Female	Male	Female
Population	911,325	1,046,025	48,851	50,940
Per cent distribution				
All ages	46.6	53.4	49.0	51.0
15–29	13.7	15.5	18.4	16.9
30–49	17.9	20.5	19.2	21.6
50–59	9.8	10.4	6.5	7.4
60 and over	5.2	7.0	4.9	5.1

* Adapted from Bureau of the Census Sample Survey, April, 1947.

TABLE 2.—*Yield of Abnormal Films and Cases of Verified Heart Disease*

Group II

	Number	Per cent
Survey population	99,791	100
Abnormal films	410	0.41
Cases examined	309	0.31
Cases verified heart disease	233	0.23
Cases previously unknown	74	0.07

Etiology. In the 233 verified heart disease cases, the most frequently occurring etiologic categories were rheumatic heart disease alone (33.5 per cent, the largest single group), hypertensive etiology alone (25.3 per cent), and the combination of hypertensive and arteriosclerotic heart disease (13.3 per cent) (table 5). When these 233 verified heart disease cases are studied from the point of view of any one etiologic category without regard to the simultaneous occurrence of other etiologic categories in the same individual (table 5), the major ones were hypertensive heart disease (47.6 per cent), rheumatic heart disease (44.2 per cent) and arteriosclerotic heart disease (26.6 per cent).

There is a difference between groups I and II in regard to etiologies of the verified heart disease cases. In group II, a larger percentage of rheumatic heart disease and a smaller percentage of hypertensive heart disease were found. There is no clear-cut explanation for this difference, unless the low level of reading of group II was less likely to turn up known cases of hypertensive heart disease.

The classification of the 74 cases of heart disease verified previously unknown fell into a quite different pattern. Classification of these 74 cases with respect to etiologies alone and in combination, or etiologies represented without regard to the occurrence of other etiologies in

TABLE 3.—*Yield of Abnormal Films, Cases of Verified Heart Disease, and Cases of Heart Disease Previously Unknown, by Age*

Group II

	Survey population	Per cent of survey population with:			Abnormal film cases examined	Per cent of examined population with:	
		Abnormal films	Verified heart disease	Heart disease previously unknown		Verified heart disease	Heart disease previously unknown
All ages	**99,791**	**0.41**	**0.23**	**0.07**	**309**	**75.4**	**23.9**
15–29	35,243	0.21	0.07	0.01	60	38.3	3.3
30–49	40,773	0.26	0.15	0.02	83	73.5	9.6
50–59	13,843	0.66	0.43	0.19	66	89.4	39.4
60 and over	9,932	1.39	0.91	0.38	100	90.0	38.0

TABLE 4.—*Yield of Abnormal Films, Cases of Verified Heart Disease, and Cases of Heart Disease Previously Unknown, by Race and Sex*

Group II

	Survey population	Per cent of survey population with:			Abnormal film cases examined	Per cent of examined population with:	
		Abnormal film	Verified heart disease	Heart disease previously unknown		Verified heart disease	Heart disease previously unknown
Total survey population	**99,791**	**0.41**	**0.23**	**0.07**	**309**	**7.54**	**23.9**
Male	48,851	0.34	0.18	0.06	116	75.0	26.7
Female	50,940	0.48	0.29	0.08	193	75.6	22.3
White	**96,203**	**0.39**	**0.22**	**0.07**	**284**	**74.6**	**22.2**
Male	47,122	0.34	0.17	0.06	109	73.4	24.8
Female	49,081	0.45	0.27	0.07	175	75.4	20.6
Nonwhite	**3,588**	**0.84**	**0.59**	**0.31**	**25**	**84.0**	**44.0**
Male	1,729	0.46	0.40	0.23	7	100.0	57.1
Female	1,859	1.18	0.75	0.38	18	77.8	38.9

the same individual, shows a marked predominance of hypertensive cases and a sharp drop in the occurrence of rheumatic heart disease (table 5). This is explained by the fact that heart disease occurring among young people is more likely to be known,[1] and the rheumatic cases occurred primarily among younger individuals.

TABLE 5.—*Etiologic Classification of Cases of Verified Heart Disease and Cases Previously Unknown.*

Group II

	Cases of verified heart diseases		Cases previously unknown	
	Number	Per cent	Number	Per cent
All etiologic classifications	233	100	74	100
Rheumatic	78	33.5	6	8.1
Hypertensive	59	25.3	39	52.7
Arteriosclerotic	17	7.3	7	9.5
Rheumatic and hypertensive	11	4.7	1	1.4
Rheumatic and arteriosclerotic	4	1.7	—	—
Hypertensive and arteriosclerotic	31	13.3	13	17.6
Rheumatic, hypertensive and arteriosclerotic	10	4.3	2	2.7
Other	18	7.7	6	8.1
Unknown	5	2.1	—	—
Major etiologic classifications (with duplications):				
Rheumatic	**103**	**44.2**	**9**	**12.2**
Hypertensive	**111**	**47.6**	**55**	**74.3**
Arteriosclerotic	**62**	**26.6**	**22**	**29.7**

It is of interest that the rate at which the various etiologic categories appeared among those who had heart disease verified previously unknown in groups I and II were almost exactly the same. This would imply that the differences in reading films at various levels of suspicion does not distort the pattern of verified heart disease previously unknown.

Benefit. Verified cases of heart disease previously unknown were studied from the point of view of possible benefit, in accordance with the definition of "Benefit" in the previous paper,[1] with the addition of hypothyroid heart disease to the "miscellaneous" category.

Of the 74 cases of verified heart disease previously unknown, there were 26 cases (35.1 per cent) who fitted into the definition of a benefited case (table 6). The 26 cases classified as benefited comprised 0.03 per cent of the base population.

TABLE 6.—*Persons Benefited among Previously Unknown Cases of Verified Heart Disease**

Group II

Etiology and Remediable Condition	Number	Per cent
All cases benefited*	26	100
Rheumatic	6	23.1
Hypertensive	7	26.9
Obesity	5	
Congestive failure	2	
Arteriosclerotic	3	11.5
Angina and obesity	2	
Congestive failure	1	
Hypertensive and arteriosclerotic	2	7.7
Angina	2	
Rheumatic and hypertensive	1	3.8
Rheumatic, hypertensive and arsclerotic	1	3.8
Congenital	2	7.7
Syphilitic	2	7.7
Myxedema	1	3.8
Pericardial tumor	1	3.8

* Does not include nine persons who believed they had heart disease when the survey films were taken, whose chest films were classified abnormal, but who were found on complete examination to have normal hearts and who were therefore believed to have been benefited.

In addition to those benefited who had verified heart disease previously unknown, there were nine individuals who believed they had heart disease at the time the survey films were taken, whose chest films were classified as abnormal, but who were found on complete examination to have normal hearts. As in Group I, these cases were considered to have been benefited by this survey. Also, as in Group I, benefit accrued to an undetermined number of cases with known verified heart disease who were returned to medical supervision.

Borderline Cases

In addition to the 233 identified cases with clinically significant heart disease among the 309 persons examined, there were 15 others in whom it was not possible to determine whether or not heart disease existed, and who were classified as "borderline cases." These include nine females and six males. Out of the 15 borderline cases, 13 did not suspect the existence of heart disease at the time of the examination. The borderline cases were identified because of suspicious findings in any one or combination of the following examinations: fluoroscopy, 12; abnormal heart sounds or murmurs, seven; electrocardiography, three; elevated blood pressure, five. As in group I, the exclusion of this "borderline" group probably minimizes the estimate of yield in this survey.

TABLE 7.—*Probable Heart Disease Status of Nonrespondent Population*
Group II

	Number	Per cent
Nonrespondents—Total	101	100
Probably Heart Disease	**40**	**39.6**
Cardiologist's report	23	22.8
Other physician's report	17	16.8
Probably Not Heart Disease	*3*	*3.0*
Cardiologist's report	1	1.0
Other physician's report	2	2.0
Status Unknown or Uncertain	**58**	**57.4**
Other physician's report doubtful	1	1.0
Person reported heart disease (unverified)	6	5.9
Person reported no heart disease	6	5.9
Person contacted—no information	25	24.8
Not found	15	14.9
Reported out of area	4	4.0
Dead, cause not heart disease	1	1.0

Nonrespondent Group

In spite of all attempts to get each of the 410 persons whose films were read as abnormal to come to the special clinic for evaluation, a total of 101 (24.6 per cent) did not. As in the study of group I, efforts were made to obtain all possible information about these people by writing to them and to their physicians.

A summary of the information so secured is given in table 7. Almost 40 per cent, 40 out of the 101 cases, had heart disease according to reports from their physicians or cardiologists. There were three persons who were said by their physicians to have no heart disease. The cardiac status of the remaining 58 persons is classified as unknown or uncertain, but six of these stated that they had heart disease. These data suggest the existence of a significant amount of heart disease in the nonrespondent group, of a magnitude similar to that in the group examined in the clinic.

LEVEL OF READING

The "level of reading," that is, the proportion of films classified by the readers as abnormal in group II, was below that of group I as discussed in the previous paper,[1] but is at approximately the same level as that reported for chest x-ray surveys conducted by the U. S. Public Health Service in other cities. Chest x-ray surveys covering more than 100,000 persons per study have been completed in nine other cities since 1947 by the U. S. Public Health Service.* Out of a total of 2,740,000 films taken, 0.66 per cent were classified as showing abnormal cardiac silhouettes, a rate only slightly higher than that observed in this study (group II). There were, however, large variations among cities. In the highest, Washington, D. C., the rate was 1.03 per cent; in the lowest, Minneapolis, the rate was 0.28 per cent.

SUMMARY AND CONCLUSIONS

1. A group of 99,791 70 mm. photofluorographic films taken for tuberculosis in the Boston Chest X-Ray Survey was read at the same time by the same readers for the existence of an abnormal silhouette of the heart or great vessels.

2. The base population of the study was distributed as to age and sex in the same manner as the population of metropolitan

* The cities are Minneapolis, St. Paul, Washington, D. C., Seattle, Cleveland, Spokane, Denver, Salt Lake City and San Diego.

Boston, with some under-representation of age groups over 50.

turned for examination. This group of 309 represents 0.31 per cent of the base population.

TABLE 8.—*Summary of Heart Disease Case Finding by Chest X-Ray Survey*
Group II

	Number	Per cent of:				
		Survey population	Abnormal films	Cases examined	Cases verified	Cases previously unknown
Survey population	99,791	100				
Abnormal films	410	0.41	100			
Cases examined	309	0.31	75.4	100		
Cases verified heart disease	233	0.23	56.8	75.4	100	
Cases previously unknown	74	0.07	18.0	23.9	31.8	100
Benefited cases	26	0.03	6.4	8.4	11.2	35.1

APPENDIX TABLE 1.—*Survey Population, Abnormal Films, Cases Examined, Cases of Verified Heart Disease, Verified Cases Previously Unknown and Benefited Cases, by Sex, Age and Sex, and Race and Sex.*
Group II

	Survey population	Yield of:				
		Abnormal films	Cases examined	Cases of verified heart disease	Verified cases previously unknown	Benefited cases
Total	**99,791**	**410**	**309**	**233**	**74**	**26**
Male	48,851	166	116	87	31	10
Female	50,940	244	193	146	43	16
15–29	**35,243**	**74**	**60**	**23**	**2**	**2**
M	18,315	31	25	10	—	—
F	16,928	43	35	13	2	2
30–49	**40,773**	**107**	**83**	**61**	**8**	**6**
M	19,183	39	29	21	3	2
F	21,590	68	54	40	5	4
50–59	**13,843**	**91**	**66**	**59**	**26**	**11**
M	6,479	35	23	21	11	3
F	7,364	56	43	38	15	8
60 and over	**9,932**	**138**	**100**	**90**	**38**	**7**
M	4,874	61	39	35	17	5
F	5,058	77	61	55	21	2
By race and sex:						
White	**96,203**	**380**	**284**	**212**	**63**	**24**
M	47,122	158	109	80	27	8
F	49,081	222	175	132	36	16
Nonwhite	**3,588**	**30**	**25**	**21**	**11**	**2**
M	1,729	8	7	7	4	2
F	1,859	22	18	14	7	—

3. Of the 99,791 films, 410 or 0.41 per cent were classified as abnormal.

4. Of those 410 individuals whose films were classified abnormal, 309 or 75.4 per cent re-

5. Of the 309 persons examined, heart disease was verified in 233 or 75.4 per cent. This group of 233 represents 0.23 per cent of the base population and 56.8 per cent of those

individuals whose films were classified as abnormal.

6. Of the 233 individuals in whom heart disease was verified, 74 or 31.8 per cent had no previous knowledge of its existence. This group represents 0.07 per cent of the base population, 18.0 per cent of those whose films were classified as abnormal, and 23.9 per cent of all persons examined.

7. Of the 74 individuals in whom heart disease was verified but was previously unknown, 26 or 35.1 per cent were "benefited." This group represents 0.03 per cent of the base population, 6.4 per cent of those whose films were classified as abnormal, 8.4 per cent of all persons examined, and 11.2 per cent of those with clinically significant heart disease.

8. Abnormal films, verifiable heart disease and verifiable heart disease previously unknown increased with advancing age.

9. A clinically significant finding was the increase in precision of film reading with advancing age of the subject—the precision increasing from 38.3 per cent in the age group 15 to 29 to 90.0 per cent in the age group 60 and over.

10. Among females, who appeared in the base population at the same frequency as males, abnormal films, verifiable heart disease, and verifiable heart disease previously unknown occurred more frequently than among males.

11. Among nonwhites, abnormal films, verifiable heart disease, and verifiable heart disease previously unknown occurred more than twice as frequently as among whites.

12. Most of the cases of verified heart disease previously unknown were classified into the etiologic categories of hypertensive, combined hypertensive and arteriosclerotic, arteriosclerotic, and rheumatic, in that order.

13. In addition to the clinically positive cases, there were 15 "borderline" cases. The characteristics of this group are discussed.

14. The nonrespondent group is known to contain a large number of verified or verifiable heart disease cases. Since these are not included, estimates based on the total population tend to understate the actual yield of this study.

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We are extremely indebted to Doctors Richard A. Bloomfield, Norman H. Boyer, Elliott Bresnick, Robert Buka, James H. Currens, James W. Dow, Robert Goldstein, Meyer Halperin, W. Proctor Harvey, George S. Kurland, John P. Rattigan, Elliot L. Sagall, Herbert S. Sise, Carlyle F. Stout, Melvin I. Sturnick, Stanford Wessler, Edwin O. Wheeler and Paul M. Zoll, who performed the clinical examinations and conscientiously recorded their findings on the standard forms; to Dr. Harold D. Levine, who read all electrocardiograms; to Doctors Paul A. Riemenschneider, Milton Elkin, James A. Glenn, Rukan Lin, Lintner E. Clark and Rudolph J. Junda, who performed the fluoroscopic examinations; to Doctor Hugo Muench and Mr. Marvin A. Schneiderman for statistical advice; and finally to the Medical Officer in Charge of the U. S. Public Health Service Survey team, Dr. Paul A. Pamplona, and his staff, without whose cooperation and assistance this entire study would have been impossible.

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Screening Tests in Mass Surveys and Their Use in Heart Disease Case Finding

By David D. Rutstein, M.D.
with illustrations by Ernest Craige, M.D.

Wherein certain principles governing screening tests for case finding in the general population are defined and the heart disease case finding studies in Boston are evaluated.

THE combined experience from mass surveys for such diseases as tuberculosis, diabetes, syphilis, cancer and heart disease has made it possible to define in a preliminary way certain principles which govern the use of screening tests in case finding in the general population.

These principles are general and apply to the use of screening tests in mass surveys for any disease. These will be discussed with particular reference to the practical use of the 70 mm. photofluorographic film for heart disease case finding by health departments, heart associations and other interested agencies, based on the data collected in the Boston heart disease case finding studies.[1, 2] No attempt will be made to outline the administrative details of the organization and establishment of a mass survey, since these have been well summarized in recent publications.[3–10]

It might be assumed that a health inventory, consisting of a complete history and physical examination, performed generally throughout the population at annual or other suitable intervals would discover disease at an early stage and assure maximum benefits of prevention and therapy. Ideally this may be true, but actually it is impractical for many reasons, including the limited number of practicing physicians, lack of orientation of undergraduate and postgraduate medical education toward early diagnosis and the preservation of health, the traditional attitude of the average layman who seeks medical attention only during illness, and the enormous expense which must be borne by the individual or, failing that, by society.

There is therefore a need for simple and inexpensive screening tests to be used in mass surveys.* Screening tests are not diagnostic but are procedures which sort out those who probably have abnormalities from those who probably do not. Mass screening consists of the application of screening tests rapidly and economically to large population groups, to sort out those who probably have abnormal conditions and refer them for diagnosis and, if indicated, for further medical care.

Case finding through mass surveys among well people should not be confused with the extensive case finding performed by the average physician in individuals who come to him after the onset of symptoms and in discovery of disease other than that suggested by patients' symptoms. The mass survey supplements his usual case finding activities by referring to him early asymptomatic disease at a stage when therapy would probably be most effective.

Evaluation of a Screening Test

Before considering the use of a test for screening purposes in a mass survey, evidence must be available that:

(1) *The test is reliable.* (a) The technical

While this paper was in preparation, the author was chairman of the Committee on Early Detection and Screening, Section on Evaluation of Scientific Data of the National Conference on Chronic Disease: Preventive Aspects. Certain portions of this paper were included by the author in the final report of that Committee, and he is deeply indebted to the members of the Committee for some of the ideas which appear in this paper.

* The definition which follows is that of the Committee on Early Detection and Screening, Section on Evaluation of Scientific Data, National Conference on Chronic Disease: Preventive Aspects.

features must be such that reproducible results can be obtained by technicians of average training. (b) Specimens collected at different times under the same conditions from the same individual must yield similar results within a narrow range of experimental error. Appropriate methods for determining such reliability are readily available.[11–13] (c) Properly qualified personnel must be available for interpretation of the test.

In the Boston Heart Disease Studies, the 70 mm. photofluorographic film is a well standardized procedure[7] which can be performed by average technicians. One unsolved problem still remaining is the exposure of the film at a specific phase of the respiratory cycle to avoid fluctuations in heart size due to changes in intrathoracic pressure during respiration.

The marked differences in yield of abnormal films in the two Boston studies[1, 2] were at least in part due to differences in training and experience of the readers in the interpretation of x-ray shadows of the heart and great vessels. It is evident that the success of a heart disease survey in a particular community will depend on the availability of properly qualified experts.

(2) *The test is valid.* The validity of the test is measured by the rate at which the result of the test is confirmed by an acceptable diagnostic procedure. Four possibilities exist when the results of the screening test are compared with those of the subsequent standardized diagnostic test: (a) "true positives": those who are selected by the screen and are also found to be positive by the diagnostic procedure; (b) "false positives": those selected by the screen who are found to be negative by the diagnostic procedure; (c) "true negatives": those who are not selected by the screen and are found to be negative by the diagnostic procedure; (d) "false negatives": those not selected by the screen but are found to be positive by the diagnostic procedure.

In order to be valid, a screening test must separate the "true positives" from the "true negatives," and keep to a minimum the number of "false positives" and "false negatives."

A mass survey divides a population into two groups, one in which the disease is likely to be present, the other in which the disease is likely to be absent. The first of these groups contains the "true positives" and the "false positives," the second the "true negatives" and the "false negatives." If the screen selects too many "false positives," an unnecessary burden is imposed on physicians and diagnostic facilities and the individual is put to needless anxiety and expense. On the other hand, if too many "false negatives" escape the screen, serious harm is done because these individuals are falsely reassured, since they are not selected by the screen and not referred for diagnostic examination. Figure 1 is an attempt to illustrate these theoretic concepts.

Special studies must be conducted to determine the validity of a screening test, since validity cannot be determined from the data usually collected in a mass screening survey. Thus, for example, in order to determine the validity of the 70 mm. film as a screening test for heart disease, in addition to the calculation of the ratio of the true positives to all positives, it is necessary to perform a complete diagnostic examination on a representative sample of those with a negative screening test to determine the ratio of the false negatives to all negatives. Such data would make it possible to determine how closely the results of the screening test approximate the true incidence or prevalence of heart disease in the study sample.

In the Boston heart disease case finding studies, the majority of those whose films were read as abnormal and who returned for examination were found to have clinically significant heart disease. Thus the number of false positives does not invalidate the practicability of the 70 mm. photofluorographic film as a heart disease case finding procedure. On the other hand, the percentage of false negatives is unknown because funds for the Boston studies did not provide for follow-up and complete examination of an unselected sample of those whose films were read as negative. Thus the ratio of false negatives to all negatives could not be calculated in the Boston studies and it therefore cannot be determined how well the screening test approximated the actual prevalence of heart disease in the Boston studies. However these studies were not designed to measure the validity of the test as defined, but rather to

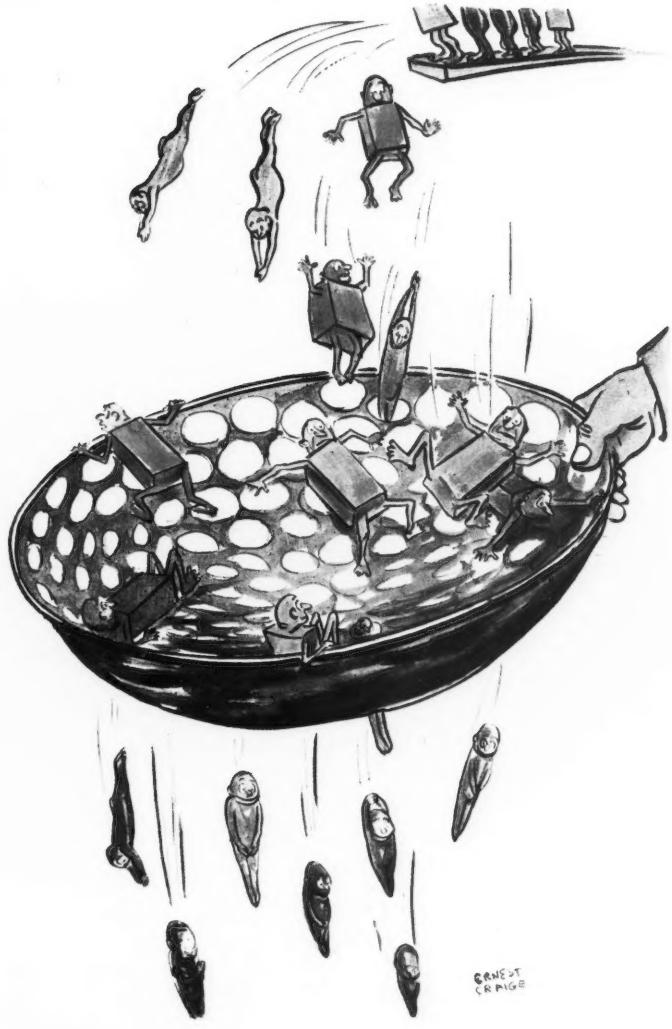

FIG. 1. The color of the figures indicates the presence (red) or absence (green) of the disease. The screen has round holes and separates the population into two groups, square figures and round figures. The square figures are the "true positives" and "false positives." The "true positives" are the square red figures, those who are selected by the screen and who have the disease. The "false positives," the square green figures, are those who are selected by the screen but do not have the disease. The round figures pass through the screen. They are the "true negatives" and the "false negatives." The "true negatives" are the round green figures who are not selected by the screen and do not have the disease. The "false negatives" are the round red figures who escape the screen but do have the disease. (*The use of color in this illustration is made possible by a grant from Wyeth, Incorporated to the publication fund of the American Heart Association.*

answer the practical question indicated in the first paragraph of the first paper of this series: "Is it possible, by means of the 70 mm. photofluorographic film as taken for tuberculosis, to identify in the general population a significant number of individuals with previously unknown heart disease who will be benefited by such identification?"[1]

If a screening test is found to be theoretically valid, there still remain the practical problems of follow-up for return for diagnosis of those selected by the screen, provision of complete diagnostic facilities and referral to medical supervision of those who are found to have the disease. Figure 2 is an attempt to illustrate these concepts.

The Boston heart disease case finding studies demonstrated the practicability of performing a heart disease survey with the 70 mm. photofluorographic tuberculosis survey film under circumstances of cooperation among the many community agencies concerned with the organization and conduct of the studies (private physicians, medical societies, visiting nurse association and the agencies responsible for the tuberculosis survey), and in which complete diagnostic facilities were established. It is not known whether this survey method is practicable if diagnostic facilities are not established, since the 70 mm. photofluorographic film in many cases may provide only suggestive evidence of cardiac abnormality which will be of little assistance to the general physician in making a definitive diagnosis of heart disease, and may make it difficult for him to justify referral of individuals with limited means to a cardiac consultant for complete diagnostic study.

Since there is implicit in a screening program acceptance of responsibility for identification and referral of all those surveyed who are suffering from clinically significant heart disease, it is unfortunate that as yet no secondary screen has been proved effective in re-examination of those with abnormal silhouettes of the heart or great blood vessels in a 70 mm. film. Attempts to use the standard 14 by 17 posterior-anterior film as a secondary screen in the survey conducted in Seattle[14] has clearly demonstrated that the standard film provides but little more information than the original survey film, is not an inexpensive procedure

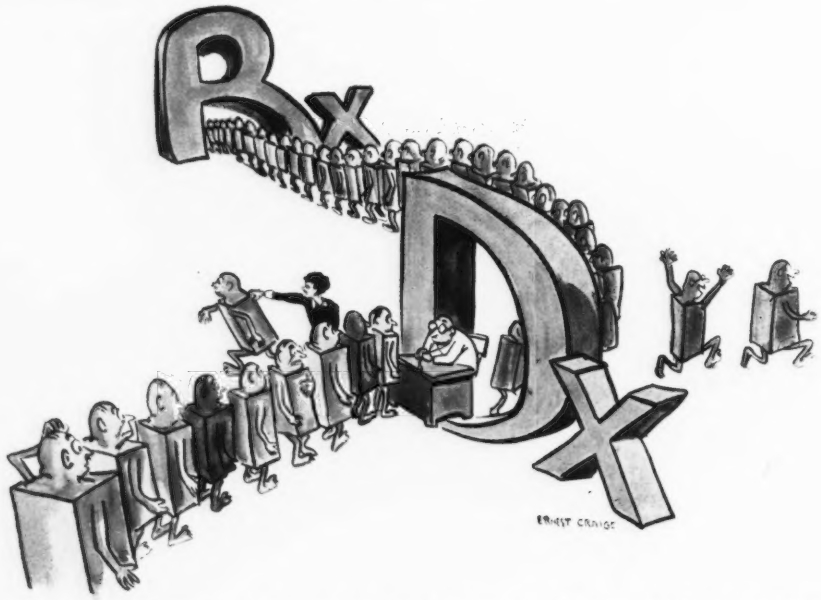

FIG. 2. The square green and red figures previously selected by the screen (fig. 1) are brought back for diagnosis (the assistance of the public health nurse is obvious). A thorough diagnostic work-up should separate the positives, the square red figures, from the false positives, the square green figures, refer the former to medical treatment while the latter are sent on their way. (*The use of color in this illustration is made possible by a grant from Wyeth, Incorporated to the publication fund of the American Heart Association.*)

and is of no real additional help in establishing a diagnosis. Until an effective secondary screen is devised, complete diagnostic facilities, particularly for those with limited means, may be necessary to provide the patient's physician with adequate information and to assure a successful survey.

Principles Governing Use of Screening Tests in Mass Surveys

When a screening test has been deemed satisfactory, its effectiveness in a mass survey can be evaluated by:

(1) *Yield*

Many methods of measurement of the yield of a screening program have been proposed, including:

(a) *The number of previously unknown verified cases of disease among the total population surveyed.* This index places emphasis on lack of previous knowledge of disease, but makes no reference to any benefit which would accrue to the discovered cases. In the first of the Boston studies, where trained and experienced radiologists read the films, there was a yield among the surveyed population of 0.9 per cent of verified cases of heart disease previously unknown.[1]

(b) *The number of persons with previously unknown verified disease benefited by referral to medical care, and the number of previously known cases not under medical care, benefited by return to it.* In the first of the Boston studies, slightly less than half of the verified cases of heart disease previously unknown were believed to have been benefited,[1] but no data were available on the number of previously known cases of verified heart disease who were returned to medical care.

(c) *The number of individuals who believe they have the disease, have a positive screening test, but are shown not to have the disease by subsequent diagnostic examination.* This yield may be considered additive to the yield as measured under (a) or (b) above. In the Boston studies, there were 18 individuals in group I and nine in group II who fell into this category.[1, 2]

(d) *The number of cases of communicable disease who are prevented from spreading their disease to the family or the community.* Heart disease is not infectious and therefore no yield can be calculated in this category.

In considering these various indexes of yield in the Boston studies, it is believed that the yield of previously unknown cases discovered and benefited in the group I study would be considered satisfactory, in comparison with yields usually obtained in mass surveys for other diseases.

(2) *Cost*

The yield of a screening program must be balanced against the cost. Cost is measured in monetary terms, which are in turn affected by the relative use of the time of professional and nonprofessional personnel.

It is impossible to calculate the cost of the Boston heart disease studies since they were organized as studies and not as routine case finding mass surveys. The monetary costs were not limited to the additional procedure of reading for heart disease the films taken for tuberculosis, the cost of the follow-up and diagnostic facilities and procedures for referral for care, but included also the cost of facilities and personnel responsible for collection and analysis of the data.

When one attempts to measure monetary costs of the Boston studies exclusive of the research costs, they are very variable depending upon which items are to be included in the calculations. Thus in these studies they included not only the basic cost of the tuberculosis survey and the additional charges imposed by heart disease case finding, but also many hidden costs in permanent personnel and facilities in the agencies responsible for the organization and operation of the studies and the amount contributed in free time by professional and lay groups. However, each community can calculate in advance the approximate additional cost of reading 70 mm. films for heart disease, and the cost of follow-up, diagnosis and referral for care, based on the particular procedures to be used in the community in question.*

* The special readers in the group I study estimated that in the average community survey for

The practical limit in the number of professional personnel, particularly physicians with highly specialized training, demands that screening tests and programs use a minimum of professional time and a maximum of the time of qualified technicians and other non-professional personnel. Moreover, the monetary cost will increase *pari passu* with the increased use of professional personnel. This statement may be paraphrased as "Never use an expert as a screen." This statement relates only to community-wide surveys and not to the very useful screening function provided by the general practitioner in recognizing disease in its early stages in patients who come to his office with early symptoms.

The screening procedure which has been most successful, that is, the 70 mm. photofluorographic film for tuberculosis, is based on this principle. In contrast, the cancer detection center demands much time from highly specialized physicians, the cost per case found is high, and this method of cancer screening has consequently been unsuccessful. In mass surveys the time of highly trained physicians is more efficiently used for precise diagnosis of disease in those already selected by the screen.

The method of heart disease case finding using the 70 mm. photofluorographic film can be performed by average technicians. Although the films require interpretation by a physician trained in the reading of such films for heart disease, the amount of "expert time" is relatively small. Thus this survey method is a practical one.

(3) *Acceptance**

Reliability, validity, yield and cost are essential criteria for the evaluation of screening tests and programs. The measurement of acceptance of the program by individuals, physicians and the community is a useful additional criterion of effectiveness of a screening program.

Acceptance of the program by the individual is measured by the proportion of the population which offers itself for screening, and then by the proportion which accepts the results of the test and follows recommendations. The patient's acceptance of the program is probably dependent, among other things, on the motivation of the individual who comes or who does not come to the screening program, and the emotional reaction to, and pain, embarrassment or hazards involved in, the testing procedures. Very little quantitative information is available on these points. Their measurement requires that scientific technics employed in the study of social attitudes and behavior be applied to the study of this problem.

Studies of the effect of mass screening programs on the case load imposed on the physician should be useful in measuring physician acceptance, which is a *sine qua non* of the success of the screening program.

Acceptance by the community can be measured by the degree of responsibility taken by official and voluntary community agencies to increase funds and facilities for care of patients discovered by the screening program, and by the spirit with which the community undertakes subsequent screening programs.

In the Boston heart disease studies, professional groups including physicians, nurses and many community agencies concerned with heart disease cooperated effectively to assure the success of the program. In these studies, patient acceptance is evidenced by the return for diagnosis of over three-fourths of those whose films were read as abnormal for size and shape of cardiac silhouette[1, 2]; however, this high rate of return for diagnosis required concerted follow-up efforts of family physicians, the Boston Visiting Nurse Association and the study group.

Special Population Groups

Although mass screening tests and programs are designed for case finding in the general population, they may be applied to special population groups: school children, industrial workers, social and racial groups and others,

heart disease, 400 to 500 films can be read in a three-hour session by a properly qualified radiologist at an approximate cost of $25 to $50.

* This section, with slight alterations in wording and emphasis and with the addition of the last paragraph, has been adapted from the report of the Committee on Early Detection and Screening, Section on Evaluation of Scientific Data, National Conference on Chronic Disease: Preventive Aspects.

when there is evidence that a high yield may be expected.

For example, in the Boston heart disease studies, higher yields were obtained in females than in males and in nonwhites than in whites. It might be expected therefore that in surveys of females or of nonwhite populations high yields would be obtained, and the yield should be highest of all in a special population group of nonwhite females.

Multiple Screening Programs*

Since the first demonstration of a successful multiple screening program[15] it has been recommended that the simultaneous application of many mass screening tests is more efficient than many individual mass screening programs. The evaluation of a multiple screening program is in principle no different from that of a screening program for a single disease. Each of the component tests and programs must be evaluated in accordance with the above criteria. In addition, special studies are needed to determine whether a particular multiple screening program increases or decreases the effectiveness of the individual component tests, and whether it is more effective than a series of individual screening programs. When these conditions have been satisfied, it may then be possible to recommend the combination of individually effective mass screening procedures into a multiple screening program.

In the Boston studies, the addition of case finding for heart disease to the tuberculosis case finding program in a sense created a multiple screening procedure. The results attained in group I justify the use of the 70 mm. photofluorographic tuberculosis survey film as a heart disease case finding procedure, whether performed individually or jointly with other established mass screening tests and programs.

* The first paragraph of this section, with minor changes in wording and with the addition of the last sentence, is adapted from the report of the Committee on Early Detection and Screening, Section on Evaluation of Scientific Data, National Conference on Chronic Disease: Preventive Aspects.

Acknowledgments

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Blood Lipids and Human Atherosclerosis

II. The Influence of Heparin upon Lipoprotein Metabolism

By Dean M. Graham, B.S., Thomas P. Lyon, M.D., John W. Gofman, M.D., Ph.D., Hardin B. Jones, Ph.D., Alexander Yankley, M.D., John Simonton, M.D., and Sidney White, M.D.

Heparin administered to humans and rabbits causes profound reorientation in the distribution of low density lipoproteins, characterized by a shift of lipoproteins of high S_f rates to those of successively lower S_f rates. The observations appear to indicate that this agent has actually caused a transformation of the former group into the latter. Heparin administered to the rabbit prevents the usual buildup of high concentration of the S_f 10–50 lipoproteins during cholesterol feeding and retards the development of atherosclerosis. In man, accompanying the redistribution of lipoproteins, there was observed a marked reduction in angina pectoris in 55 of 59 patients studied who presented this symptom. The relation between the heparin effect upon lipoproteins and its effect upon angina cannot be assessed at present.

A HYPOTHESIS that atherosclerosis is a disease associated with or caused by an error in the metabolism of fat and other lipids has been previously presented.[1] The evidence supporting this hypothesis consists in the demonstration of the existence of certain special classes of lipoprotein molecules associated with atherosclerosis in several experimental animal species and in the human developing or manifesting atherosclerosis.[1–3]

The further study of these lipoproteins as well as several other lipoprotein species has revealed[3, 4] that essentially all of the blood lipids (including fat, cholesterol, cholesterol esters, and phospholipids) exist in the blood only in the form of structural entities within several of these lipoprotein molecular classes. Current work is directed toward an understanding of the factors involved in the defect which results in the abnormal elevation of such molecules as the S_f 10–20 lipoproteins in certain individuals. Each lipoprotein, which can be identified in its native state by the ultracentrifugal analysis of serum, presumably has a different functional role in lipid metabolism. Its concentration in the blood is the resultant balance between formation and utilization at any particular steady state of physiologic activity. Physiologic factors already reported to influence serum lipoprotein levels include (a) dietary intake of fats and cholesterol, (b) thyroid function, (c) experimental adrenal cortical hyperactivity (rabbit only), (d) age, (e) sex, (f) pregnancy.[3, 5] Several errors in lipid metabolism have now been classified by the ultracentrifugal analysis of serum lipoproteins. Such are manifest in (a) atherosclerotic state, (b) nephrosis, (c) xanthoma tuberosum, (d) biliary obstruction, (e) acute hepatitis,[6] (f) certain cases of diabetes, (g) hypothyroidism, (h) hypercholesterolemia, (i) xanthelasma.[7] In addition, there are certain bizarre, but characteristic, ultracentrifugal lipoprotein patterns which are seen in presumably normal individuals, but are as yet unclassified.

All individuals show some of the lipoprotein species in the serum. The individual variations encountered are derived from two variables, (a) the number of different lipoprotein species present, (b) the relative abundance of the different lipoproteins in a single serum. A variety of evidence[3] suggests that the typical "normal" of humans shows one or more lipoprotein species in the range up to 6 S_f units (including the S_f 2, S_f 4, S_f 6 lipoproteins). An analogous situation exists in the rabbit, chicken and dog with minor differences in the S_f rate of the normally occurring lipoproteins. In atherosclerosis and certain other lipid metabolic derangements there exist in addition varying concentrations

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of lipoproteins in the classes S_f 8, S_f 10, S_f 13, S_f 17, S_f 17–20, S_f 20–40, S_f 40–40,000. In the range S_f 8–S_f 40, the higher members of the group of lipoproteins make their appearance in serum only when appreciable levels of all lower members are present. However, the relative abundances of these various lipoproteins are variable from one disease category to another. In the range S_f 40–40,000 there are also characteristic patterns associated with disease states, but lipoproteins of the S_f 40–40,000 class also represent part of the alimentary "lipemia" of normals. Elevation of the S_f 10–30 range of lipoproteins has been shown to be essentially universally a part of the development of atherosclerosis in the human as well as other species. However, at least certain of the higher members may also be involved in this disease, but as the variability in concentration in a given individual approaches the variability of groups, they have not been used as a correlative guide.

As an extension of our studies of the factors involved in the maintenance of the levels of the various serum lipoproteins, it has now been found that heparin can produce a profound alteration in the lipoprotein pattern in a manner which may prove of value in the further understanding and management of atherosclerosis. Heparin, of course, has long been used clinically in the therapy of thromboembolic disease, but not for any possible influence it might have upon metabolic factors leading to atherosclerosis.

Hahn[8] reported that heparin abolished alimentary lipemia in vivo, but not in vitro. Weld[9] showed that the phenomenon is not restricted to any particular vascular bed by perfusing various body regions with heparinized lipemic plasma. Recently Anderson[10] has shown that the turbidity of lipemic plasma may be cleared in vitro by mixing lipemic plasma drawn before heparinization with that drawn five minutes after heparinization. He hypothesized an "anti-chylomicronemic" factor which results from heparin injection and discussed the possibility of a heparin-phospholipid complex being a surface active agent responsible for the clearing of lipemic plasma. Waldron[11] reported that other anticoagulants (sulfonated polysaccharides and pontamine fast pink B.L.) produced effects similar to heparin.

Experimental

A single injection of sodium heparin intravenously in the cholesterol-fed rabbit produces dramatic changes in the lipoprotein spectrum, characterized in general by a *decrease* in concentration of molecules of the high S_f classes, with a concomitant *increase* in concentration in those of the lower S_f classes.

The association of these two changes suggests a progressive conversion of the higher S_f lipoproteins into those of lower S_f rates. An immediate response is observed within five minutes in the lipoproteins of the highest S_f classes, with successive changes in those of the lower S_f classes, with maximum effect being observed at about three hours. Subsequently the pattern "reverts" to its initial state in approximately 24 hours.

To obtain some evaluation of the chronic effects of heparin administration upon the evolution of the pattern of serum lipoproteins and the associated aortic atheroma, 40 rabbits were fed cholesterol and cottonseed oil. These animals were divided into two groups, matched as closely as possible as to age, sex, weight, and strain. One group received heparin injections of 10 to 25 mg. per rabbit per day; the other group served as a control. Pairs of heparin and control animals were killed and autopsied after three to eight weeks of cholesterol feeding. Of 20 rabbits maintained on heparin, 17 showed no gross atherosclerosis and three did show atherosclerosis. Of the 20 controls, five showed no gross atherosclerosis and 15 did show gross atherosclerosis. The indicated suppression of atherosclerosis by heparin administration is significant (the probability of no significance of this result is less than 0.01). Heparin so administered suppressed the development of the S_f 10–50 class of molecules to 15 to 50 per cent of the levels observed in the control animals fed the same amount of cholesterol and oil. It is highly likely that this explains the observed protection afforded these rabbits by the administration of heparin.

In man, even more striking effects are seen following heparin administration. The progres-

sive changes in the spectrum of lipoproteins following intravenous injection of 100 mg. of sodium heparin are shown in figure 1. This patient, a survivor of a myocardial infarction, showed initially high levels of lipoproteins in the S_f 10–20 class, as well as in the S_f 20–100 class. Within 15 minutes there was essentially a "wipe-out" of lipoproteins from S_f 20–100, associated with an *increase* in the concentration of the S_f 10–20 class. Then, during the next six hours there was an over-all shift within the S_f 10–20 class, so that the S_f 12–20 lipoproteins were markedly reduced in concentration to below their original level, while the S_f 10–12 and S_f 6–10 lipoproteins increased in concentration over the initial level. Progressively over a period of 24 hours the entire pattern reverted toward the initial pattern, although there was still a lower S_f 12–20 level than initially. This same general effect has been observed in each of 30 subjects (normal and myocardial infarction) studied in this manner, the only variations observed being in the degree of response and in the time relationships of the sequence of events which occur. Dosages ranging from 15 to 100 mg. of sodium heparin intravenously have proved definitely effective, although graded dosage in a single patient requires further evaluation.

In vitro attempts to alter the lipoprotein pattern by addition of heparin have failed in all of numerous trials. However, samples of plasma from heparinized patients have been found effective in altering the lipoprotein spectrum of serum drawn from the same individuals before heparin administration or of serum of other individuals. Thus it appears that the injection of heparin results in the in vivo production of an "active principle" capable of producing these conversions of lipoproteins in vitro. The result is similar to the studies of the "anti-chylomicronemic" factor of Anderson. In an effort to elucidate the mechanism of the effect on lipoproteins, we have found that the "active principle" appears to reside in the ultracentrifugal globulin region. The serum albumin fraction and the low density lipoprotein group both appear inactive. Globulin fractions from postheparin plasma when incubated with earlier postheparin plasma appear to cause further changes in the lipoprotein distribution in such plasma in vitro. We have as yet been unable to detect any of the "active principle" in serum from individuals who had not received heparin, although it is conceivable that such a factor may circulate at low concentration.

In an effort to determine the effect of a maintained heparin level on the serum lipoprotein pattern we have made some studies of individuals receiving repository heparin.* Figure 2 shows the effect of heparin repository in the same patient whose studies are shown in figure 1 with intravenous heparin. It is noted that in four hours with repository heparin this patient lost essentially all of her lipoproteins above S_f 10, representing in essence a reversion to a "normal" lipoprotein pattern. After 24 hours there was a partial return of S_f 10–20 molecules (50 per cent), but a much lower fractional reappearance in the S_f 20–100 class of molecules. (Even after two and four days there is a significant depression of the S_f 10–20 level.)

A series of 20 patients have received intravenous heparin at intervals varying from two to 14 days. There appeared to be no reduction of ability of patients to show the response described in figure 1, even after numerous heparin injections. A small proportion of the patients showed depression in S_f 10–20 levels which persisted for the full three to 14 day intervals between intravenous injections of heparin, but in general the levels observed three to 14 days after injection showed no average trend toward reduction. In this particular series samples were drawn throughout just prior to each new heparin injection. From what has been observed in the 24 hour period following such injections, we may anticipate that, averaged over the entire period between injections, the S_f 10–20 level may have been appreciably lower than its preheparin value. However, we do have direct evidence that with a suitable heparin dosage schedule, chronic lowering of the serum S_f 10–20 levels can be obtained.

One patient studied over a one month period, who had shown a maintained S_f 10–20 depression for the three day interval between heparin injections, showed a slow progressive

* Lederle Repository Heparin.

rise approaching his original S_f 10–20 levels over a one month period after cessation of heparin injections. In a patient with xanthoma tuberosum who had an initial S_f 12–20 level of 500 mg. per 100 cc., there was a slow progressive reduction to 150 mg. per 100 cc. over a four week period of daily injections of 100 mg. of heparin. On cessation of the heparin there was a rise to 400 mg. per 100 cc. in the course of two weeks. On resumption of daily heparin injections the S_f 12–20 level again fell progressively to 150 mg. per 100 cc.

An incidental and unexpected clinical observation made by Lyon and Yankley in the course of this investigation was that 55 out of 59 patients with moderate or severe angina pectoris reported marked relief from this symptom with a drastic decrease in nitroglycerin requirement soon after the period of initiating heparin injections. Forty-five patients in this group had previously had a documented myocardial infarction. Eight of the remaining 14 patients were hypertensives with cardiographic evidence of left ventricular hypertrophy. Four others showed cardiographic evidence consistent with coronary insufficiency, and the re-

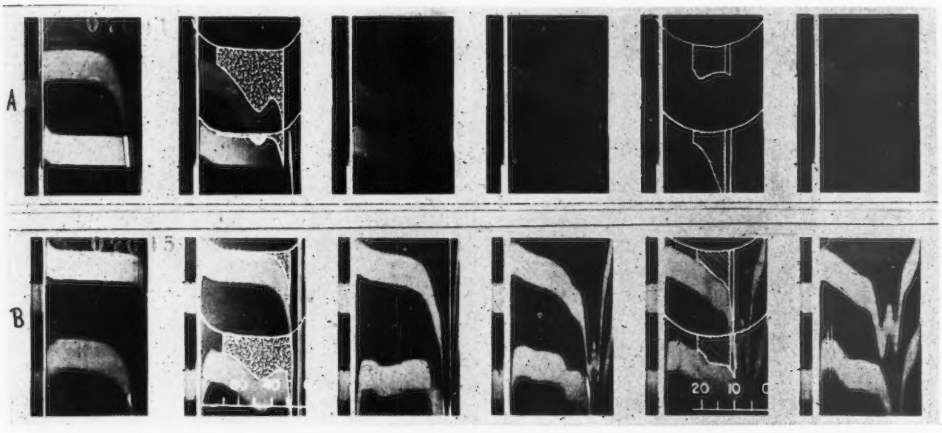

FIG. 1. The Effect of a Single Intravenous Injection of Heparin on Human Low-Density Lipoproteins. The accompanying ultracentrifugal flotation patterns show the progressive changes in the lipoproteins of a 63 year old female patient with coronary artery disease treated with a single 100 mg. dose of heparin given intravenously. In all the figures successive frames are taken at 0, 6, 12, 22, 30, and 38 minutes after full rotor speed of 52,640 rpm has been reached. Frames 2 and 5 in figure 1*B*, lower pattern, are ruled for the calculation of the S_f rates of any peak appearing in these frames, respectively. These rulings can be used to calculate S_f rates in the corresponding frames of the other figures. All *stippled* areas represent the measure of the S_f 20–100 class of lipoproteins, all *cross-hatched* areas represent the measure of the S_f 12–20 class of lipoproteins.

Figure	Time after heparin	S_f 12–20	S_f 20–100
		(*mg.* %)	(*mg.* %)
1*A* upper pattern	Preheparin	167	530
1*A* lower pattern	20 minutes	239	50*
1*B* upper pattern	6 hours	128	52
1*B* lower pattern	26 hours	143	344

* The sample recorded in 1*A* lower was ultracentrifugally concentrated only to three-fourths the level in the other samples. Hence the measured area from the diagram was corrected for this in preparing the tabulation of results. It is seen that while the six hour postheparin sample shows an S_f 12–20 level not over 25 per cent lower than the preheparin sample, there is a marked shift in distribution of the lipoproteins of the S_f 12–20 class toward the lower ranges of this class.

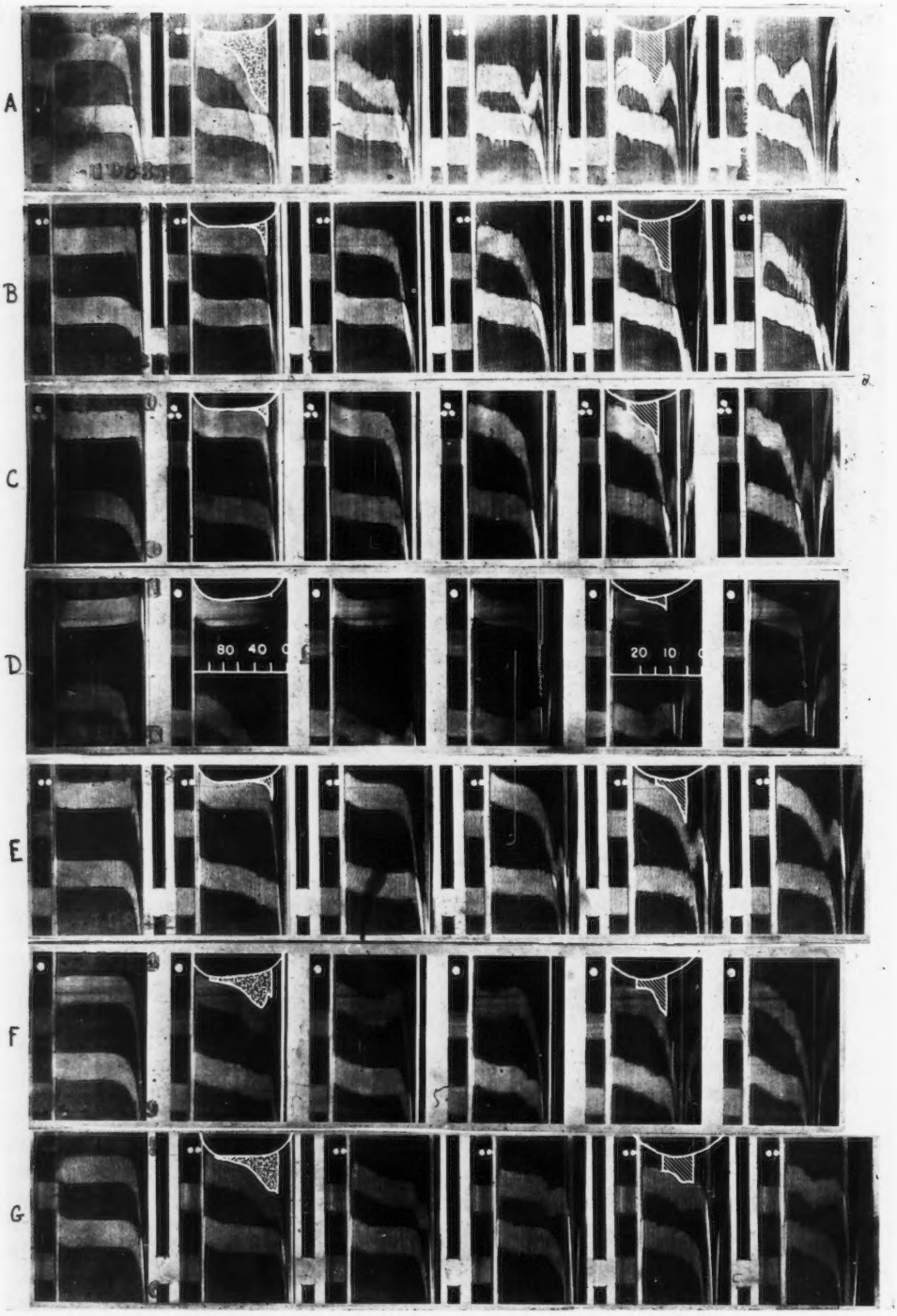

FIGURE 2

maining two cases showed normal records. These patients have been treated for periods of from one to eight months with one or two injections of 50 to 100 mg. of intravenous or intramuscular sodium heparin per week. The relief from angina usually was noted after the first few injections. In those patients who have been under treatment for over six months (17 cases) there has been no evidence of a loss of efficacy of the heparin. Reports on the effect of heparin in relieving pain of myocardial infarction and as a coronary vasodilator have appeared in the literature.[12, 14] However, the presently reported responses in angina pectoris have been observed with small, intermittent doses of heparin (50 to 100 mg.) given at intervals of several days in ambulatory patients. The size of the dose and the infrequency of injections speak against either a vasodilator or antithrombotic basis for the response. All of seven patients whose severe angina had been relieved by heparin injections complained of return of anginal symptoms when saline placebos were injected instead of heparin.

We are cognizant of the many difficulties in evaluating objectively efficacy of drug relief of angina. However, the striking character of the response in patients with relatively fixed anginal patterns and nitroglycerin requirements, plus the loss of response when saline placebos were used would appear to militate against the response being in any way psychogenically determined. Extended studies of this response are in progress now. We are not able at this time to provide any suggestion of a possible relation of the heparin effect on blood lipoproteins to that in relieving angina pectoris, although there may be such a relation.

Discussion

Heparin appears to act profoundly and rapidly in altering the blood lipoprotein spectrum. Shifts among the lipoproteins are observed both in man and the rabbit from molecules of the higher S_f classes to those of successively lower classes in times of the order of minutes to hours following a single heparin injection. The decrease in concentration of a particular S_f range

FIG. 2. The Effect of Heparin Repository on Human Low-Density Lipoproteins. The accompanying ultracentrifugal flotation patterns show the progressive changes in the lipoproteins of a 63 year old female patient with coronary artery disease treated with a single 200 mg. dose of repository heparin. In all the figures successive frames are taken at 0, 6, 12, 22, 30, and 38 minutes after full rotor speed of 52,640 rpm has been reached. Frames 2 and 5 have been ruled in figure 2*D* for calculation of the S_f rates of any peak appearing in that frame. The ruling of frame 2 in figure 2*D* may be used to calculate S_f rates in frame 2 of any of the other figures. Similarly the ruling of frame 5 in figure 2*D* may be used to calculate S_f rates in frame 5 of any other figures. All patterns shown represent two different sera run simultaneously in the ultracentrifuge. In each figure only the *upper* pattern is involved in this study. The *lower* pattern is from another individual and is to be completely disregarded. All *stippled* areas represent the measure of the S_f 20–100 class of lipoproteins, all *cross-hatched* areas represent the measure of the S_f 12–20 class of lipoproteins.

Figure	Time after heparin	Sf 12–20	Sf 20–100
		mg. %	*mg. %*
2*A*	Preheparin	197	357
2*B*	70 min.	147	18
2*C*	3 hours	102	14
2*D*	4 hours	21	0
2*E*	6 hours	83	18
2*F*	24 hours	81	160
2*G*	72 hours	107	164

In addition the figures reveal a great increase in the concentration of lipoproteins of the S_f 6–10 and S_f 10–12 classes accompanying the decrease in concentration of lipoproteins in the classes above S_f 12. The change in concentration of all lipoproteins between S_f 12 and S_f 100 in four hours after heparin administration is 533 mg. per cent. Assuming a plasma volume of approximately 2500 cc., this represents a minimum of 13 Gm. of lipoprotein cleared by the action of 200 mg. of heparin in the repository form.

of molecules, accompanied by an increase in the concentration of molecules in the next lower S_f classes suggests that the former molecules may be actually transformed into the latter by the influence of heparin. This appears to occur in several successive stages over a period of hours. This represents one of the first clues on the possible interrelationships of the various classes of lipoproteins of serum. Inasmuch as the lipoproteins of the S_f 17–100 classes represent in man the major glyceryl ester (fat) bearers of serum, the observed interconversion accentuated by heparin may represent steps in the normal pathway of transport and metabolism of fat. It is appropriate to consider the possibility that heparin itself, or some substance of similar properties, may normally be involved in the physiologic interconversion of lipoproteins. Thus, in individuals who usually show high levels of S_f 10–20 and S_f 20–100 lipoproteins, there may be a blockage in the utilization pathways of such molecules (possibly due to deficiency of a heparin-like substance), so that a piling up in concentration of such molecules occurs in the blood. In supposedly normal individuals (especially young adults and children of both sexes), all these molecules, if present, are in very low concentration, which would be expected if utilization pathways were greatly facilitated in these individuals.

As reported by Anderson for the in vitro clearing of alimentary lipemia by in vivo heparinized plasma, the present work indicates that heparin in free form does not directly induce any alteration in lipoprotein spectrum. However, plasma from heparinized patients contains a factor that is effective. This factor resides in the ultracentrifugally determined globulin fraction and induces changes in vitro which simulate, at least in part, the changes in lipoproteins which follow in vivo administration of heparin. Further search for such an "active factor" in the sera of "normal" individuals who show low levels of S_f 10–100 lipoproteins appears warranted. If present, such a factor might be anticipated at very low concentration, from the negative results of our searches for it to date. Again, such a factor might not normally reside in appreciable concentration in plasma, but might be called forth in response to lipid loading.

Heparin administered to rabbits protects the animal from development of atherosclerosis under circumstances which otherwise induce atherosclerosis. Since the protective effect of heparin is accompanied by a suppression of development of high levels of the S_f 10–50 lipoproteins, the observation strengthens the previously reported evidence linking these molecules with atherosclerosis, and further suggests the value of maintaining low levels of these molecules in prevention of experimental atherosclerosis. The effect of lowering similar classes of molecules in the human on progression of the clinical manifestations of atherosclerosis is being evaluated.[13]

The dramatic relief of angina pectoris by intermittent heparin administration parallels the profound effect of this substance upon lipoprotein metabolism. However, at this time we have been unable to *demonstrate* that these two simultaneous effects are actually related. It may be that the relief heparin provides in angina pectoris is due to its vasodilator or to its antithrombotic activity. The effect on angina pectoris is seen with small doses of heparin and persists much longer than the anticoagulant effect of the doses used. Currently under study are the effects of heparin in several diseases which are marked by extreme elevation of lipoproteins of the S_f 10–100 classes (such as nephrotic syndrome, hypothyroidism and xanthoma tuberosum) in 55 of 59 cases.

Summary

1. Heparin administered to rabbits and man causes profound reorientation in the distribution of low density lipoproteins, characterized by a shift of lipoproteins of high S_f rates to those of successively lower S_f rates.

2. Heparin administered to cholesterol-fed rabbits prevents the development of high levels of S_f 10–50 lipoproteins and retards the development of atherosclerosis in such animals.

3. Following heparin administration the plasma contains an "active principle" associated with the ultracentrifugal globulins, which produces similar re-orientation of the lipoprotein spectrum in vitro.

4. Heparin added directly to serum is ineffective in vitro.

5. Intermittent heparin administration to patients with severe angina pectoris results in dramatic and uniform relief from this symptom for periods of several days beyond a single injection in 55 of 59 cases.

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Effect of Small Doses of Heparin in Increasing the Translucence of Plasma during Alimentary Lipemia

Studies in Normal Persons and Patients Having Atherosclerosis

By William J. Block, M.D., Nelson W. Barker, M.D., and Frank D. Mann, M.D.

Heparin administered intravenously increases the translucence of plasma during alimentary lipemia. This apparently is solely a physical change. This article reports observations concerning this phenomenon in normal persons and atherosclerotic patients. For purposes of maximal sensitivity, exceedingly small amounts of heparin are used, and distinct differences between the normal and the atherosclerotic individuals are noted, with the atherosclerotic failing to clear well on the same empiric dose of heparin as the normal persons. An unexpected observation was that the normal men developed a significantly greater degree of lipemia than did normal women after ingestion of the same fat meal.

In 1943 Hahn[1] made the observation that intravenous injection of heparin increases translucence of plasma during alimentary lipemia. This work has been confirmed and extended,[2–5] but has received relatively little attention. This reaction occurs only in vivo, but once initiated in vivo it will continue in vitro, the effect lasting 18 to 24 hours.[3, 4] Apparently this is solely a physical change of blood lipids, quantitative determinations of blood lipids remaining unchanged. The work of Anderson and Fawcett[4] suggests the possibility that the mode of action may be through the formation of a highly surface-active heparin-phospholipid complex.

Our interest in this phenomenon was aroused as the result of recent reports suggesting that the physicochemical state of blood lipids may be related to the development of atherosclerosis. These include the chylomicron hypothesis of Moreton[6]; the suggestive significance of the cholesterol:phospholipid ratio as indicated by the work of Ladd and co-workers[7] and of Ahrens,[8] and the possible significance of the giant particles observed by Gofman and co-workers[9] in work with the ultracentrifuge. The recent work of Bragdon[10] in experimental transfer of atherosclerosis by transfusion further suggests the importance of the physical state of plasma lipids. The present study was conducted to learn whether or not this peculiar effect of heparin occurred in equal degree in normal persons and patients who had atherosclerosis.

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Abridgment of thesis submitted by Dr. Block to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

Method

In brief, the plan of study was to produce alimentary lipemia in our subjects and then observe the effect of intravenous injection of heparin on the translucence of the plasma.

Fat Meal. The subjects were given 240 cc. of 40 per cent cream (40 per cent butterfat by weight) to which 8 Gm. of cocoa and 16 Gm. of sugar had been added, making a total of 97.5 Gm. of fat. This proved to be a fairly palatable mixture. The subjects were required to fast after a normal supper the evening before. The fat meal was given in the early morning between 8 and 9 a.m. Smoking and drinking water were permitted on the morning of the test. The same quantitative fat meal was used for all subjects. The effect of fat on gastric motility and secretion[11] and the variation in normal persons was appreciated.[6, 12] Our purpose was to observe the effect of heparin on the alimentary lipemia which developed three hours after the fat meal, whatever the degree.

Heparin. A solution of the sodium salt of heparin was diluted so that 1 cc. contained 100 Toronto units (approximately 1 mg.). This dilution was made by adding 10 cc. (10,000 Toronto units or approximately 100 mg.) of the original solution to 90 cc. of 0.85 per cent sterile sodium chloride solution with 10 capillary drops of liquefied phenol added as a preservative.

A dose of 3 mg. (3 cc.) injected intravenously just failed to restore completely the translucence of the plasma during alimentary lipemia in a pilot study of normal men. Two additional milligrams of heparin then did produce maximal translucence in the plasma of these persons. Accordingly this minimal dosage of 3 mg. was chosen on the presumption that it would probably be a more sensitive test to elicit possible differences between the various subject types than would a larger dose. This dose was given empirically to all subjects of this study three hours after the ingestion of the fat meal.

Blood Specimens. Three blood specimens were drawn as follows: just prior to the ingestion of the fat meal; three hours after the fat meal, just prior to administration of heparin; three and one-fourth hours after the fat meal (15 minutes after the injection of heparin). For the purpose of spectrophotometric determinations, 4.5 cc. of each specimen of blood were mixed with 0.5 cc. tenth molar solution of sodium oxalate, and all these specimens were centrifuged simultaneously for 15 minutes at 2,500 rpm in a size 2 International Centrifuge, within one hour after the last blood specimen was drawn.

Quantitative plasma lipid determinations, including cholesterol, cholesterol esters, phospholipid, fatty acids and total lipids, were made on all fasting specimens.* Ten cubic centimeters of oxalated blood were used for this purpose. In agreement with previous investigations, the heparin was found to produce no significant change in the chemical values for blood lipids; therefore the chemical determinations were done only on the fasting specimens in most subjects.

Plasma cholesterol was determined by the method of Bloor[13] adapted for use with the Coleman Spectrophotometer.

Plasma cholesterol esters were determined by the method of Bloor and Knudson[14] adapted for use with the Coleman Spectrophotometer.

Plasma phospholipid was determined by the method of Youngburg and Youngburg[15] as modified by Maclay.[16]

Plasma total lipids were determined by the method of Bloor.[17]

Plasma fatty acids were determined by subtracting the value of total cholesterol from that of the total lipids.

* All chemical determinations were performed in the Laboratory of Clinical Chemistry.

Measurement of Translucence of Plasma. This measurement was made one hour after the last specimen had been drawn. It was essential to observe accurately this one hour interval because, once initiated in vivo, this peculiar action of heparin continues in vitro.[4] The plasma specimens were read in the Coleman Junior Spectrophotometer at 650 mμ against a water reference using a cuvette 10 mm. in diameter. Results were read on the optical density scale of the instrument. For the purposes of convenience and clarity the term "clearing" henceforth will be used to designate increased translucence of the plasma following injection of heparin.

Calculation of Percentage Clearing of the Lipemia. The value for the fasting specimen was subtracted from the values for the other two specimens, thus correcting the readings to indicate the decrease in translucence due to alimentary lipemia. The postheparin value was then subtracted from the preheparin value to obtain the difference due to clearing.

The ratio of this difference to the preheparin value × 100, thus the percentage clearing, was used as an expression of clearing of the lipemia. In a few instances the postheparin plasma became slightly clearer than the fasting specimen, or on the other hand slightly less translucent than the preheparin specimen. For simplicity, the former instances were recorded as 100 per cent clearing and the latter 0 per cent.

Subjects. The following groups were studied in this report: (1) 20 normal women of ages ranging from 19 to 42 years with no evidence of vascular disease; (2) 23 normal men of ages ranging from 27 to 46 years with no evidence of vascular disease; (3) 27 atherosclerotic male patients ranging in age from 33 to 72 years, all of whom had unequivocal evidence of atherosclerosis, which consisted of either clinical and electrocardiographic evidence of recent myocardial infarction or clearly demonstrable arteriosclerosis obliterans of the lower extremities; (4) five atherosclerotic female patients ranging in age from 50 to 66 years. Criteria for diagnosis were the same as under (3).

Results

The degree of translucence of plasma following a fatty meal is shown in table 1. The normal women in this study showed excellent clearing, averaging 84 per cent (table 2). The range was from 62 per cent to 100 per cent. Quantitative plasma lipids were all essentially within normal limits (tables 3 to 8). Cholesterol:phospholipid ratios were all less than unity, varying from 0.569 to 0.890, and averaging 0.715.

TABLE 1.—*Degree of Translucence of Plasma following a Fatty Meal*

Group	Number	Optical Density of Plasma		
		Highest	Lowest	Average
Normal women	20	0.308	0.041	0.151
Normal men	23	0.548	0.088	0.294
Atherosclerotic male patients	27	0.680	0.051	0.201

TABLE 2.—*Percentage Clearing of Plasma following Injection of Heparin*

Group	Number	Percentage clearing			Number clearing less than 40 per cent
		Highest	Lowest	Average	
Normal women	20	100	62	84	0
Normal men	23	100	28	74	2
Atherosclerotic male patients	27	100	0	38	16

TABLE 3.—*Levels of Plasma Cholesterol in Milligrams per 100 cc.*

Group	Number	Highest	Lowest	Average
Normal women	20	230	127	173
Normal men	23	254	127	181
Atherosclerotic male patients	27	383	143	232

TABLE 4.—*Levels of Plasma Cholesterol Esters in Milligrams per 100 cc.*

Group	Number	Highest	Lowest	Average
Normal women	20	150	75	107
Normal men	23	172	72	112
Atherosclerotic male patients	27	262	84	143

TABLE 5.—*Levels of Plasma Phospholipid in Milligrams per 100 cc.*

Group	Number	Highest	Lowest	Average
Normal women	20	355	175	244
Normal men	23	289	182	240
Atherosclerotic male patients	27	345	162	257

Normal men showed a degree of decreased translucence three hours after the fat meal that was significantly greater (mean difference 0.143 ± 0.034*) than that of normal women of the same age group (table 1). This was entirely unexpected, for, on the contrary, it would seem that in the women, who were almost all smaller than the normal men, a lesser degree of translucence would develop than in the men. The plasma of the majority of normal men cleared well, averaging 74 per cent as a group (table 2). Some cleared completely, but two cleared less than 40 per cent. One of these two men showed a reversal of the cholesterol:phospholipid ratio (1.04). Otherwise quantitative plasma lipids were essentially normal.

TABLE 6.—*Plasma Cholesterol:Phospholipid Ratios*

Group	Number	Highest	Lowest	Average
Normal women	20	0.89	0.569	0.715
Normal men	23	1.04	0.506	0.775
Atherosclerotic male patients	27	1.17	0.692	0.897

TABLE 7.—*Level of Plasma Fatty Acids in Milligrams per 100 cc.*

Group	Number	Highest	Lowest	Average
Normal women	20	442	231	292
Normal men	23	494	236	320
Atherosclerotic male patients	27	615	200	394

TABLE 8.—*Level of Plasma Total Lipids in Milligrams per 100 cc.*

Group	Number	Highest	Lowest	Average
Normal women	20	652	358	465
Normal men	23	621	374	501
Atherosclerotic male patients	27	1,106	367	625

The group of atherosclerotic male patients showed no unusual decrease of translucence after the fat meal. The average fell between that for normal men and that for normal

* The value after the ± is the standard error of the difference. A difference which is two or more times its standard error is generally considered statistically significant.

women. There was, however, a significant difference in the degree of clearing following injection of heparin. Sixteen of the 27 patients cleared less than 40 per cent, and the average clearance for the group was only 38 per cent, despite the fact that two patients cleared completely (100 per cent). Although there was no absolute correlation, and despite two exceptions, on the whole the patients that cleared best were in the older age group, more than age 55 years, younger patients showing poor clearance.

Although many in this group had normal plasma lipids, seven patients had elevated levels of plasma cholesterol and 10 patients had elevated total plasma lipids. The averages of all lipid determinations were greater than those of normal men and women. Six patients had reversal of the cholesterol:phospholipid ratio. The average approached unity, and was greater than that for the normal persons of this study. It can be readily seen that reversal of the ratio was infrequent, although a definite trend toward unity was seen. The fact that many atherosclerotic patients had normal plasma lipids shows that this finding is not at all inconsistent with the diagnosis of atherosclerosis.

There seemed to be no significant correlation between the percentage clearing due to heparin and the individual or total lipid content or the cholesterol:phospholipid ratio of the fasting samples. The results of scatter diagrams did not warrant further statistical survey of this matter.

The group of female atherosclerotic patients is too small to enable one to draw any conclusions. The degree of decreased translucence due to alimentary lipemia was not striking. One cleared less than 40 per cent after injection of heparin. Quantitative plasma lipids were normal in this patient, although elevated in another. Cholesterol:phospholipid ratios were less than unity. This group, because of its small size, will not be tabulated.

Comment

The mechanism of this peculiar action of heparin in changing the physical state of blood lipids during alimentary lipemia is not known. As stated before, the possible formation of a heparin-phospholipid complex has been suggested. This would mean a highly surface-active, hydrophilic substance similar to phospholipid alone.

It is interesting that in this study a significant difference in the response to intravenous injection of heparin during alimentary lipemia exists between normal male and female subjects and male atherosclerotic patients. This difference in clearing cannot be attributed to a difference in age, for nine of the 11 patients in this group who showed more than 40 per cent clearing (including one who showed 100 per cent) were more than 55 years of age. Actually there appeared to be, if anything, an inverse relationship between age and the abnormal resistance to clearing, but the size of the group was insufficient to test this statistically. Concerning other factors, two patients in the group had cardiac failure and both cleared well (100 per cent and 70 per cent). Several patients who cleared well and several who did not were receiving dicumarol.

The data appear to show a true relationship between atherosclerosis and resistance to clearing of lipemic plasma by heparin. This resistance in these patients could be an expression of an abnormal inhibition or neutralization of heparin. This may be consistent with variation in heparin tolerance and requirement in different individuals as regards anticoagulation[18–20]; in this respect atherosclerotic patients have been found to require more heparin.[21] The resistance may be due to a basic abnormality in the state of plasma lipids. Possibly both factors play a role.

The fact that normal men showed a significantly greater decrease of plasma translucence during alimentary lipemia than did normal women of the same age group following the same fat meal may be significant.

Quantitative determinations of plasma lipid showed variations. All normal subjects were essentially within normal ranges, although one normal man had a reversed cholesterol:phospholipid ratio. The majority of the atherosclerotic patients had essentially normal lipids, but some were elevated. Average values of those even with normal lipids were greater than in normal subjects. The cholesterol:phospholipid

ratio averaged lowest in normal women, next lowest in normal men, highest in the atherosclerotic patients, although still less than unity.

Summary

The effect of intravenous injection of heparin on the translucence of plasma during alimentary lipemia in normal subjects, both male and female, and in male atherosclerotic patients has been observed. In this study, in normal men, a decrease in translucence of the plasma developed following a standard fat meal which was significantly greater than that which developed in normal women of the same age group. In the majority of instances male atherosclerotic patients showed much less clearing of alimentary lipemia following a small dose of heparin than did the normal male and female subjects.

Fasting quantitative lipid determinations were essentially normal in all normal subjects, although one showed a reversed cholesterol: phospholipid ratio. The majority of atherosclerotic men had normal lipids, although some were elevated. Several had reversed cholesterol: phospholipid ratios, and the average approached unity as compared with the normal.

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The Distribution of Body Fluids In Congestive Heart Failure

I. Theoretic Considerations

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The pathogenesis of congestive heart failure is discussed. Experimental evidence is cited to support the thesis that abnormalities in the distribution of body fluids may affect circulatory and renal function, and hence may be a cause as well as an effect in the complex sequence of events leading to the congestive state. Emphasis is placed upon alterations in cellular metabolism which may lead to such disturbances in body fluids and so through various mechanisms, cellular, humoral, and circulatory, may modify the volume regulation of the body.

DURING the past few years the clinical entity, congestive heart failure, has been subjected to a great deal of physiologic reinterpretation. This reinterpretation has been due for the most part to the development of new technics for the study of circulatory dynamics, of renal dynamics, and of transfers of body water and electrolytes. It is now appreciated that this syndrome is one involving a complex series of events often occurring over a considerable period of time between the initiating factors and the final condition of venous congestion and edema of many tissues. Indeed, the lack of correlation between immediate and measurable abnormalities of cardiac function and the congestive state have led some writers to challenge the importance of the factor of "cardiac damage" and to speak of the state as "congestive circulatory failure" or simple "congestive failure." Nevertheless, as Starr[1] points out, "congestive failure occurs with great frequency in persons with damaged hearts," and this fact strongly supports the conclusion that disease of the heart is either an initiating factor, or at least an important contributory factor, in the etiology of this syndrome. Our problem, therefore, is the elucidation of the events which lead from cardiovascular dysfunction on one hand to the edematous state on the other.

From new data many investigators have emphasized especially the role of the kidney in the development of congestive failure, and impaired glomerular filtration has been considered by some to be the principal renal abnormality. Yet much evidence points as well to abnormal function of the kidney tubules, and this in turn suggests the possible involvement of the several endocrine glands which normally share in the regulation of renal tubular transfers of salt and water. The problem, therefore, devolves in part on ascertaining how the kidney operates in the regulation of the fluid balance of the body and how this regulation is disturbed in the condition of congestive failure.

Evidence is accumulating from the study of normal organisms that variations in the volume and composition of fluids in tissues other than the heart or kidney affect the fluid balance of the body. Intake (thirst and appetite) and renal output of water and electrolytes are so adjusted to each other that the volume of body fluids is maintained in a steady state. The means by which changes in the water and solute content of various tissues help to effect this homeostatic control of total body fluid volume are essentially unknown. Yet such knowledge would appear to be of paramount importance to the study of congestive failure. Furthermore, it is now recognized that the differential distribution

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of solutes, and therefore of water, between cells and their surrounding mediums, are maintained by energy derived from metabolic processes within the cells.[2] Any role which may be played by the state of fluid distribution in particular tissues, or in tissues in general, in the fluid balance of the body, is inevitably linked to reactions which take place in the intracellular phase.

For these reasons it seemed advisable, in undertaking an investigation of the distribution of body fluids in congestive failure, to consider in the light of present experimental evidence the various relationships which may obtain between the circulation, the kidney, and the fluid content of other tissues, especially as related to

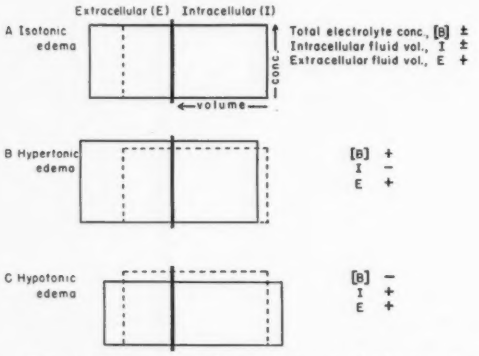

FIG. 1. Diagram of theoretic types of abnormalities in volume and total electrolyte concentration of the several phases of body fluids, in edema. Broken lines represent the normal pattern.

cellular metabolism. Such theoretic consideration is undertaken in the hope that it might place in proper perspective the role of abnormal fluid distribution as a *cause* as well as an effect in the chain of events leading to the accumulation of edema.

The discussion of this complex problem is perhaps best accomplished by considering the evidence bearing on the following four questions: (1) What are the abnormalities of body fluid distribution in congestive failure which are due to (a) the disease itself, or (b) attempted therapy (for example, mercurials)? (2) To what extent are these abnormalities in congestive failure due (a) to changes in circulatory dynamics directly, (b) to changes in renal function, (c) to modifications of cellular metabolism? (3) Do these abnormalities in body fluid distribution in turn affect (a) circulatory function, (b) renal function? (4) If so, in what ways? Although the experimental evidence bearing on these questions is fragmentary, it is extensive enough to justify the opinion that, in addition to circulatory and renal dynamics, factors of cellular metabolism and tissue fluid distribution must be considered in the pathogenesis of congestive heart failure.

In view of these questions certain observations were made on patients with heart disease and edema. These observations are reported in the succeeding papers.[3–5] The data which are presented by no means provide the answers, but they do again emphasize that the questions outlined above are pertinent to the problem of congestive failure.

DISTRIBUTION OF BODY FLUIDS IN CONGESTIVE FAILURE

Expansion of the extracellular fluid is the predominant abnormality. The edema of cardiac failure has usually been considered to be an isotonic expansion of extracellular fluid (fig. 1*A*). Evidence for this rested upon the observation that the products of diuresis are mostly water, sodium, and chloride in the same relative proportions as in extracellular fluid.[6] Various deviations from this simple pattern have been reported. It has been reported[7] that in congestive failure sodium is retained by the kidneys to a greater degree than is chloride; if the disparity in clearances of these two ions is not due to the simultaneous administration of ammonium chloride, an increase in the extracellular concentration of bicarbonate should ensue. Indeed, many patients with congestive failure have been found to have an elevated concentration of serum bicarbonate,[8–10] a finding which indicates that some type of disturbance in acid-base equilibrium occurs in relation to the disease or to its treatment. If more sodium were reabsorbed in order to retain water as part of the dehydration reaction,[11] as suggested by Peters,[12] the concentration of sodium in serum and extracellular water should tend toward or beyond the upper limits of normal, depending on the relative rates of water ingestion and

sodium reabsorption. Conversely, if water is retained in excess of sodium, the serum and extracellular sodium concentration should be depressed. Hyponatremia has been reported or implied from the existence of hypochloremia in congestive failure, but such hyponatremia (and hypochloremia) are almost always observed to follow prolonged courses of treatment with mercurial diuretics.[13, 14] Since water shifts across cell membrane when the sodium concentration is changed in extracellular fluid in normal subjects,[15] such a phenomenon immediately implicates the intracellular phase in the fluid abnormality of edema at least under certain circumstances of therapy (figs. 1*B* and 1*C*).

Intracellular content of water and of certain electrolytes may also be abnormal. Disturbances in intracellular fluid have been found in many disease states, including water deprivation and dehydration, starvation, gastrointestinal fluid loss, metabolic alkalosis, acidosis due to diabetic coma and renal insufficiency, and in diseases involving hypo- and hyperfunction of the adrenal cortex. In most of these states the fluid abnormalities described have been depletion or excess of intracellular sodium and intracellular potassium. In considering intracellular fluid disturbances, other components in addition to these must be taken into account. With present methods of study it should be possible to describe changes in the following: (1) transfers of water across the cell boundary according to the dictates of variations in the effective osmolar concentrations in the two phases, (2) transfers of potassium into and out of cells, (3) transfers of sodium into and out of cells, (4) transfers into and out of cells of other anions, particularly phosphate and possibly chloride, and (5) changes in osmotic activity of solutes within the cells (fig. 2). Abnormal transfers of some of these constituents have been described in congestive failure. Newman and co-workers[16] found that potassium was retained in excess of nitrogen in a number of cardiac patients during diuresis of edema fluid. Fox and co-workers[17] have reported the occurrence of diuresis following the administration of hypertonic solutions of sodium and potassium and have postulated that in congestive failure there is a hypotonic overhydration of the intracellular phases. Other workers[18-20] have also described the uptake of potassium in cardiacs, but more complete information has yet to be obtained concerning abnormalities in the major fluid constituents of the intracellular phase in patients with congestive heart failure.

There are regional differences in fluid distribution in congestive failure. This statement needs no further support than the common observation that the edema is usually greater in the dependent portions of the body. This disparity of distribution presumably is due to the effect of gravity on the hydrostatic pressure in veins and capillaries in these regions, although other factors such as local anoxia may play a role.

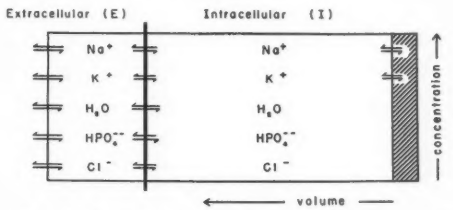

FIG. 2. Diagram of transfers of certain constituents of the body fluids between cells, extracellular fluid and environment. Arrows between the several phases indicate only the directions of movement of the individual constituent; no quantitation of rate or magnitude of transfer, or of concentration, is implied. The cross-hatched area on the right represents fractions of intracellular solute that are osmotically inactive and as such may be considered to be transferred out of the aqueous phase of cellular fluid.

In summary, from this brief review it appears that the evidence in regard to the first question may be stated as follows. The common fluid abnormality in congestive failure is retention of extracellular electrolytes and water. Intracellular disturbances in respect to volume of water are suggested by the occurrence of an abnormally low electrolyte concentration (hyponatremia) but this phenomenon is probably the result of therapy rather than of the congestive failure *per se*. Intracellular disturbances in content of electrolytes, especially potassium, have been documented, but the relationship of these abnormalities to the disease or to the state of nutrition has not been established. Finally, abnormalities in the regional distribution of body fluids are present in this condition.

Given these disturbances of body fluid distribution in congestive heart failure, we turn to the second question, namely, how are they initiated by cardiovascular and renal dysfunction.

Circulatory and Renal Factors in Edema

This discussion deals with the type of congestive failure which develops over a prolonged period of time in patients with heart disease. It is recognized that congestive failure may develop acutely: (1) in cardiac patients as a result of a sudden redistribution of fluids without an increase in total body weight, for example, acute pulmonary edema; and (2) in patients without heart disease who in various ways acquire abruptly a large increment of total body water and salt. However, we are concerned with the patient with a damaged heart who accumulates edema more slowly, that is, who over a protracted period has a total output that fails to equal the total intake of fluids. In some manner this must result from a functional impairment of the damaged heart.

"Backward failure" and "forward failure" have both been proposed to account for congestive heart failure. For many years the sequence of events as deduced from Starling's[21] original hypothesis was held to describe adequately the development of edema. Essentially, this sequence was as follows: cardiac failure with diminished output, elevation of venous and capillary hydrostatic pressure, transudation of fluid from plasma to interstitial spaces causing edema, diminution of plasma volume, and reduction of sodium and water excretion by the kidney. In 1943 Starr and co-workers[22] and subsequently Warren and Stead[23] proposed another sequence of events: cardiac failure with diminished output, decreased renal blood flow and rate of glomerular filtration, decreased excretion of sodium and water, increased plasma volume, increased venous and capillary pressure, transudation and edema. This hypothesis[1, 22, 23] rests in part on evidence that fall in cardiac output, expansion of blood volume, and the development of edema may precede the rise in venous pressure in congestive failure, and in part on the demonstration of changes in renal hemodynamics. However, Peters[12] has questioned the validity of the evidence for high blood volumes in this condition. He points out that in any case Starling's theory in regard to the distribution of fluid across the capillary membrane must obtain and challenges the primary place of the renal dysfunction in the sequence of events. Thus, the role of the changes in renal hemodynamics is still the subject of considerable controversy.

Neither "backward failure" nor "forward failure" accounts for the lack of correlation between the output of the heart and the development of congestive failure. These two theories have been based on the assumption that an absolute diminution in cardiac output to below the average normal range is the critical impairment of function in the diseased heart. Yet signs and symptoms resembling congestive failure are known to occur in the presence of abnormally high levels of cardiac output, as in beriberi and thyrotoxicosis.[24, 25] Decompensation and recompensation may occur in a patient with very little change in the level of cardiac output.[26] For these reasons other factors would appear to be involved which relate the output of the heart to demands which the body places upon it.

Disparity between the output of the heart and the metabolic demands of the body may be the basic cause of the signs and symptoms of congestive heart failure, including edema. This concept, stated by Altschule,[27] is suggested to explain the lack of correlation between the absolute level of cardiac output and the degree of congestive failure. Such a concept receives further support from the observation that recompensation of the failing heart can occur when an unchanged or falling cardiac output is associated with a lowering of the basal metabolic rate.[28] This demand on the heart by the body can be stated in terms of oxygen requirement, although other metabolic factors conceivably may be involved. Evidence has been presented by Little[29] of inverse correlations between the degree of congestive failure and the ratio of oxygen supply to oxygen consumption, and also between central venous pressure and mixed venous oxygen tension. Briggs and associates[26] found that oxygen A-V differences decreased with recompensation. These observations sug-

gest that lack of oxygen (hypoxia) in one or more areas of the body is a next step in the sequence leading to congestive failure. Whether or not hypoxia may influence directly at the cellular level the retention of fluid in tissues (see below), it at least has an effect on the general and regional dynamics of the circulation. Regional changes in circulation are known to result when the blood volume and oxygen supply are inadequate for the entire body.[30, 31] These regional differences in circulation may influence the accumulation of edema in a variety of ways, as set forth in the last section of this paper. But diminished blood flow to the kidney with consequent impairment of glomerular filtration has been considered by the proponents of "forward failure" to be the major factor in the development of congestive failure.

Diminished glomerular filtration and a fixed rate of tubular reabsorption of sodium do not alone explain the retention of salt and water. The studies of Merrill,[32] Mokotoff, Ross and Leiter,[33] and others, have shown conclusively that renal blood flow and glomerular filtration are markedly reduced in many patients with congestive failure. Leiter[34] and Wesson, Anslow and Smith[35] have used these findings to support the hypothesis that a constant maximal rate of reabsorption of sodium obtains in the distal renal tubule and hence, when filtration of sodium diminishes, the excretion rate of the ion falls. This hypothesis is difficult to substantiate or refute since the amount of sodium rejected by the tubule and excreted is such a minute fraction of the amount filtered and reabsorbed that it falls well within the error of measurement of the latter. However, considerable evidence has accumulated that tubular transfers are likewise important in determining the abnormally low rate of sodium excretion in heart failure. In the patients studied by Merrill and Mokotoff and associates the correlation was very poor between excretion rate and filtration rate, and other workers[16, 26, 36-38] have found that the excretion rate may vary considerably with the loss or gain of edema without much change in the rate of glomerular filtration. In normal subjects, when renal plasma flow has been varied independently of filtration, the excretion rate of sodium has been found to correlate more closely with the former than with the latter.[39] It would appear, therefore, that abnormalities of renal tubular transfers are integral to the pathologic function of the kidney in edema.

Tubular transfers are abnormal in congestive failure and may be influenced by circulatory, humoral and cellular factors. The relationship of circulatory insufficiency to glomerular function in the kidney is much more easily understood than its relationship to that of the tubules. To what extent is there a direct effect of circulatory factors on the renal tubules and to what extent is there an indirect effect mediated through one or more endocrine glands? Hormonal regulation of such transfers in the normal kidney is well established. The antidiuretic hormone (ADH) of the posterior pituitary gland regulates water reabsorption, and at least one of the adrenal cortical steroids, closely resembling, if not identical with, desoxycorticosterone acetate (DCA), affects the reabsorption of sodium and potassium. Abnormal amounts of antidiuretic substance and of adrenal cortical steroids have been found in the urine of patients with congestive heart failure[40-42] but it has not yet been shown conclusively that the failure of the kidney to excrete water or salt is mediated primarily through either of these hormones. A variety of circulatory factors have been investigated for their effects, direct or indirect, on renal tubular function in this condition. Renal venous hypertension has been shown experimentally by Blake and co-workers[43] to result acutely in increased renal tubular reabsorption of sodium. The importance of the time factor in this phenomenon was emphasized by Hwang and associates[44] who demonstrated that with prolongation of the renal venous hypertension over a period of a week or more, the rate of sodium excretion returned to control levels. Wilkins and colleagues[45] have found a decreased excretion of sodium following venous congestion of the limbs. The observations of Blake and coworkers suggest a direct effect of renal circulation on the tubule, those of Wilkins and his associates suggest a humoral as well as a direct circulatory effect. Anoxia might logically be thought to be a factor but the experiments of

Berger and colleagues[46] indicate that in the normal subject systemic anoxia accelerates rather than retards the excretion of sodium and water. However, these also were acute studies; protracted anoxia in certain cases has been associated with the accumulation of edema, which in turn was relieved by the administration of oxygen.[1, 47] In fact, both the degree and the duration of anoxia must be considered before a clear cut idea can be entertained as to its effect on sodium metabolism. Again, the immediate receptor of this stimulus may be in the kidney or elsewhere. Perhaps alterations in the fluids of various tissues are shared by the tubular cells of the kidney and so directly effect tubular transfers of electrolytes and water. Thus, despite the many possibilities which have been considered, one of the key questions remaining unanswered is how the kidney tubular cells know how to regulate their transfers of electrolytes and water in terms of the distribution of fluids in tissues at a distance, and how this process functions abnormally in the patient with congestive heart failure.

In summary, it is apparent that much remains to be learned concerning the relative roles of cardiac and renal dysfunction in congestive heart failure. The absolute level of cardiac output does not correlate with the degree of edema, and cannot explain it on either a "backward" or a "forward failure" theory. An output of the heart which is inadequate in relation to metabolic demands would appear to be a primary factor leading to secondary changes in circulatory dynamics in several regions of the body. Renal retention of salt and water results from more than a circulatory disturbance causing a diminished glomerular filtration; tubular transfers are involved and these are conditioned by humoral and cellular, as well as by circulatory, factors.

Effects of Abnormalities of Body Fluids on Circulatory and Renal Function

What are the properties of the body fluids and their component parts which effect their regulation by the kidney? It is perhaps stating the obvious to say that changes in the volume and composition of body fluids produce effects on renal function. Yet, as indicated above, little is known as to just how renal regulation of body fluid volume takes place. Wolf[48] has recently reviewed this problem and points out that most of the emphasis in the past in investigation of renal function has been placed upon the regulation of concentration of solute rather than of volume of solvent. Clearly the regulation of body content of electrolytes is intimately tied up with that of water, but there is some evidence that such renal regulation is more than a function of concentration, ionic or total osmolar, in circulating plasma. Warren and Stead,[23] Borst[49] and Dock[50] have related the renal regulation of body fluid volume to maintenance of an adequate cardiac output. Aside from the problem of how these two factors act upon one another, there are other difficulties involved in this concept which have been reviewed by Lewis and co-workers.[51] These include the observation referred to above, that there may be no correlation between the level of cardiac output and the degree of edema in congestive failure, and that alterations of cardiac output in other conditions are not associated with corresponding changes in the renal excretion of water and electrolytes. Therefore, in addition to cardiac output, it is necessary to look for certain characteristics of the body fluids, such as regional composition and volume, which may influence their regulation by the kidney.

Cellular hydration, interstitial volume, and intracranial volume appear to condition the renal excretion of water and electrolytes. Under conditions of water deprivation and dehydration, sodium and chloride are increasingly reabsorbed by the renal tubule despite rising concentrations of these ions in the plasma.[11] Peters[12] has termed this the "dehydration reaction" and suggests that in congestive failure a similar stimulus mistakenly occurs. The precise nature of the stimulus is not apparent, although it may be related to a contraction of the effective circulatory volume; in any case it is certainly not the concentration of electrolytes in the extracellular fluid and plasma. Seldin and Tarail[52] have shown in normal subjects that the increased excretion of sodium which occurs during certain types of osmotic diuresis occurs

only following the injection of solutes which are essentially excluded from cells, such as free glucose and mannitol, and not following the injection of urea which is freely diffusible and does not cause cellular dehydration. These authors interpret these data to indicate that the excretion of sodium under these circumstances is conditioned not merely by the total osmolar concentration of solute in the tubular urine but also by the effects of the specific solute injected on cellular hydration of tissues elsewhere in the body. It should be pointed out that in these experiments expansion of extracellular fluid volume was an invariable accompaniment of the contraction of the intracellular fluid and hence may be a significant variable. Green and Farah,[53] in experiments on the renal effects of sodium loading in dogs, have presented evidence that the rate of tubular rejection of this ion is more closely related to the rate of cellular dehydration produced by the load imposed, than to the concentration or absolute amount of sodium in the extracellular fluid. Welt and Orloff[54] studied the effect on water and sodium excretion of variations in plasma volume, plasma colloid osmotic pressure, and interstitial fluid volume, as produced by injection of human albumin in various concentrations. They found that elevation of plasma volume without elevation of the colloid osmotic pressure led to an increased rate of excretion of water and possibly sodium, whereas a decrease in sodium excretion resulted from raising the colloid osmotic pressure as well. The data were interpreted to indicate that the renal excretion of water and sodium is influenced by not only plasma volume and colloid osmotic pressure but possibly also by interstitial fluid volume. Harrison and co-workers[51] have found evidence that compression of the neck veins is associated with increased excretion of sodium by the kidney, indicating that some attribute, possibly volume, of the intracranial fluids may condition the renal excretion of electrolytes. The experimental manipulations in normal subjects, cited above, of Seldin and Tarail and of Welt and Orloff lead to different results in edematous patients.[55, 56] This suggests that in the edematous state additional factors influence renal function. But, nevertheless, experimental evidence of this kind indicates that in some way, directly or indirectly, changes in the distribution of fluids in the body, including expansion of plasma and interstitial volumes and contraction of intracellular volume, effect changes in renal function.

Body fluid distribution and circulatory system are closely interrelated because of the role of the latter as the "mixing apparatus." There is an interrelationship between body fluid distribution and circulatory dynamics as well as between the former and renal function. Primary changes in the circulation may induce secondary changes in the distribution of body fluids, and vice versa. This is best understood if one considers the multicompartmental character of the body fluids. It is an error to conceive of the extra- and intracellular fluids as single homogeneous solutions contained, so to speak, in a beaker (fig. 1*A*). The extra- and intracellular fluids are parts of many different tissues widely separated throughout the body, and are connected by extended lines of communication, the circulation (fig. 3). The circulation is the "mixing apparatus" and its efficiency determines the constancy of composition, or homogeneity, of the fluid phases (the extracellular directly and the intracellular indirectly). It is not surprising, therefore, that disturbances in circulatory function may lead to differences in composition and distribution of fluid in various parts of the body. It is, perhaps, less obvious, but nevertheless true, that disturbances in the composition and distribution of body fluids may affect the function of the circulation.

Primary changes in the circulation may cause secondary disturbances in the fluid content of tissues, for example, "prerenal deviation." Changes in the circulation which affect fluid distribution are many and some may be enumerated. Increased venous pressure due to obstruction or gravity leads to local transudation of fluid from plasma to interstitial spaces.[57] Diminished cardiac output, arterial occlusion, or peripheral vascular collapse may produce tissue anoxia and so disturb electrolyte equilibria which are maintained by oxidative reactions; for instance, potassium may leave and sodium enter cells.[58–61] Under such circumstances cellular water may or may not be re-

leased, according to the dictates of the changes in the effective osmolar concentration of solutes in the two phases. Collapse of the circulation may result in the retention of water and solutes in the body because of the simple failure of transport of such substances to the organ of excretion.[62] Borst[49] and Wolf[48] have inveighed against the validity of this concept of "prerenal deviation." Wolf states that there is little evidence that all parts of the body fluids are not readily accessible to renal regulation. Yet in the instances just set forth it appears to the authors that the integrity of the circulation stands between the fluids of peripheral tissues and the action of the kidney upon them. Hence circulatory dysfunction may lead to "prerenal deviation," at least in the sense that the time that is required for their regulation by the kidney is greatly increased. Such a concept is easily understood by the clinician who observes, for instance, certain effects of transfusion on a patient in shock, such as absorption of subcutaneous pools of fluid (hypodermoclyses, for example), reestablishment of urinary flow, correction of acid-base disturbances (for instance, chloride acidosis) and excretion of accumulated metabolites.

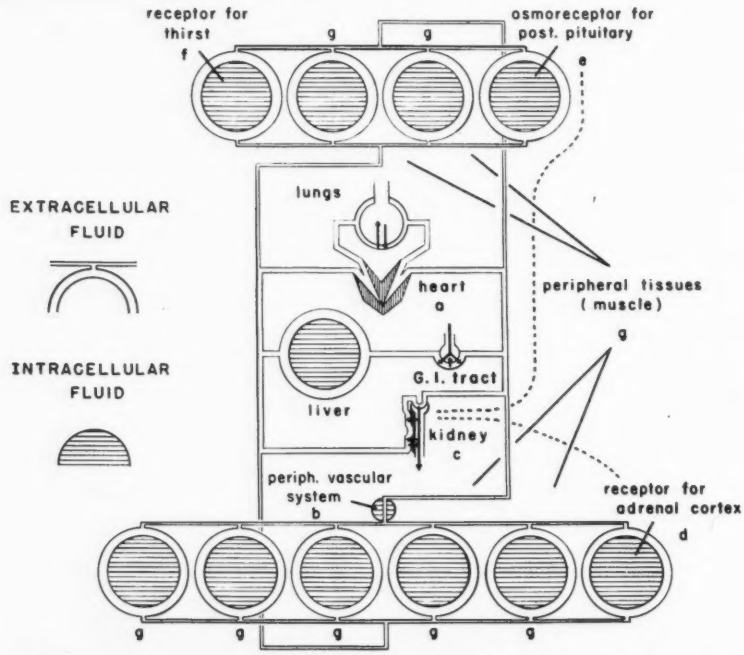

FIG. 3. Diagram of the intracellular and extracellular fluids of the body, including pathways of circulation in the latter, and sites of transfers with the external environment.

The multicompartmental character of the body fluids is emphasized, as well as the role of the circulation as the "mixing apparatus" for the extracellular fluid. Transfers of the various constituents between the two fluid phases, diagrammatically shown in figure 2, take place in each of the many units of the body fluids. Loci of some of the intracellular fluids in which changes in composition may affect, directly or indirectly, the distribution of fluids in the body as a whole, are indicated by letters *a* to *g*, inclusive.

Primary changes in the body fluids may affect the circulation; for example, sodium depletion causes diminution of cardiac output and renal blood flow. Changes in the body fluids which affect the circulation are also numerous and not completely understood. Obviously, alteration in the volume of that portion of the extracellular fluid contained within the vascular system, the plasma, is intimately related to circu-

latory function. Expansion of blood and plasma volume, as when whole blood or concentrated albumin is administered, may result in an increase in cardiac output in patients in shock[63] and in renal blood flow in normal subjects.[64, 65] Contraction of the blood and plasma volume may lead to diminution of cardiac output, arterial pressure, renal blood flow, or generalized peripheral vascular collapse.[66] Abnormalities in the extra- and intracellular fluids as a whole, are less well understood in regard to their effect on the circulation. Diminution of extracellular fluid volume resulting from dehydration, and especially from sodium depletion, is closely associated with collapse of the circulation. That this relationship is not due alone to the concomitant fall in plasma volume is suggested by the following experimental evidence obtained in dogs by one of the authors and his associates.[62, 67] Shock due to sodium depletion was more profound than that due to dehydration alone; in the initial phases of sodium depletion the cardiac output and arterial pressure fell abruptly well before the drop in plasma volume; restoration of extracellular fluid and plasma volume alone, by the infusion of isotonic glucose solutions, did not restore the cardiac output. From these data it appeared that changes in total electrolyte concentration, and therefore in intracellular fluid volume, had some effect on the circulation, peripheral or central, other than that mediated through the plasma volume. Changes in the volume or composition of intracellular fluid have effects on the circulation under a few other circumstances. Depletion of intracellular potassium, and excess of cellular sodium in the myocardium, as produced by overdosage of desoxycorticosterone, has been reported to produce lesions which might result in acute congestive heart failure.[68] The same phenomenon has been suggested to occur in other types of clinical potassium deficiency.[69, 70]

In summary, from these observations it would seem that the third question asked in the introduction can be answered in the affirmative; that is, that body fluid distribution can affect both circulatory and renal function. The question remains, does this occur in congestive failure, and if so, how?

Various Ways in Which Abnormalities of Fluid Distribution May Play a Role in the Pathogenesis of Congestive Failure

Abnormalities of fluid distribution in many tissues may modify, secondarily, the circulatory and renal factors in congestive failure. Circulatory factors must be primary in the etiology of congestive failure in patients with heart disease, at least in a temporal sense; the place of such factors in the more immediate sequence of events is still open to discussion. Factors of fluid distribution which may modify secondarily the circulatory disturbances have received less attention from investigators. From the preceding discussion, however, it should be apparent that some of these possible modifications occur on the cellular level. Accordingly, in the discussion which follows, particular emphasis will be placed on disturbances in cellular metabolism and fluid composition of various tissues, as they may play a role in the pathogenesis of congestive failure.

For purposes of discussion some of these hypothetic relationships are listed in table 1. *Primary Relationships* are concerned with cardiac dysfunction and its immediate sequelae. Cardiac dysfunction may be defined as a cardiac output which is inadequate in relation to the demands of the body. A and B are the essential relationships of "forward" and "backward" failure. C introduces the possibility that a relatively inadequate output of the heart may modify cellular metabolism by failing to maintain an adequate supply of oxygen and other nutrients or to remove completely the products of catabolism. Given this last result of an inadequate cardiac output, a series of *secondary* relationships is postulated. In the first place, such a state of modified cellular metabolism may lead to alteration of effective blood flow and effective blood volume between various regions of the body. And in the second place, it may disturb the exchanges of electrolytes and water between the cells and extracellular fluid in various tissues. Such disturbances in turn may promote the edema of congestive failure by direct effect on the cardiovascular system and on the peripheral tissues, or indirectly by humoral effects on the kidney. Some of the possible sites of these cellular disturb-

ances are diagrammatically indicated by the letters *a* to *e* in figure 3. Obviously we are dealing with a set of complex interrelationships in which secondary effects may further augment primary causes. Some of these interrelationships which would create vicious cycles are indicated in table 1 (by cross references in brackets).

TABLE 1.—*Hypothetic Relationships of Circulatory, Renal, and Body Fluid Factors in the Production of Edema in Congestive Heart Failure.*

I. Primary relationships
  Relatively inadequate cardiac output and:
  A. diminished glomerular filtration
  B. venous congestion
  C. modified cellular metabolism
    (failure to supply oxygen and other nutrients, failure to remove products of catabolism, etc.)
II. Secondary relationships
  A. Modified cellular metabolism and regional alterations in effective blood flow and blood volume:
    1) Relatively decreased renal blood flow [IA]*
    2) Relatively decreased peripheral blood flow [IIB4]
    3) Relatively decreased cerebral blood flow and volume
      Stimulation of a blood and interstitial volume receptor [IIB2]
  B. Modified cellular metabolism and alterations in cellular electrolytes and water:
    1) Impairment of myocardial and peripheral vascular function (a)†, [I].
    2) Increased tubular reabsorption of Na and H_2O [IB]
      a) DCA from adrenal cortex (d)
      b) ADH from posterior pituitary (e)
      c) Local stimuli in renal tubular cells (c)
    3) Fluid intake increased in relation to output (thirst and appetite) (f) [IB]
    4) Direct effect on peripheral tissues (g)
      ? Cellular depletion of potassium
      ? Cellular overhydration due to increased cellular osmolarity.
III. Tertiary relationships
  A. Modifications of I and II by therapy.
    1) Mercurials, acting on IIB:
      2c, ?2b, ?3, ?4

* Figures in brackets indicate possible interrelationships.

† Letters in parentheses refer to cellular loci diagrammatically represented in figure 3.

Alterations in regional blood flow may promote edema. Anoxia is known to result in changes in blood flow between various regions of the body.[30] The stimulus presumably is initiated on the cellular level and is effected in part through reflex vasomotor activity and in part through direct local action. Diminution of renal blood flow may cause a further fall in glomerular filtration rate and so promote retention of salt and water. Diminution of peripheral blood flow should lead to increased hypoxia of the peripheral tissues (see below). Harrison and co-workers,[51] as mentioned above, have found that intracranial congestion is associated with increased excretion of salt and water by the kidneys. On the basis of their experimental work they postulate a "volume receptor" in the cranial cavity which conditions the renal excretion of salt and water. These workers suggest that in congestive heart failure intracranial blood volume is diminished by redistribution of blood to other parts of the body, and so stimulates the receptor to initiate the renal retention of salt and water. To such a receptor changes in blood volume or in interstitial fluid volume are more likely to be the stimulus than are changes in cell volume. In either case, alterations in the circulation in this region of the body may be a critical factor.

Aside from influencing the blood flow to various regions of the body, modified cellular metabolism leading to disturbances in water and electrolyte content of the cell may be a secondary factor in the pathogenesis of congestive failure by a variety of mechanisms.

Secondary tissue fluid changes may affect directly function of the heart or peripheral vascular system (fig. 3, *a* and *b*). This possibility is supported by the hemodynamic response cited above[62, 67] to the experimental depletion of sodium leading to hyponatremia and intracellular overhydration. Potassium depletion of the myocardium has also been reported to lead to acute congestive failure.[68–70] However, it has not been established that such a vicious cycle occurs in the congestive failure attendant upon chronic valvular disease of the heart; coronary occlusion with myocardial infarction is a special case in this regard.

Increased renal tubular reabsorption of sodium

and water is probably the result of secondary changes in the cells of the receptors of certain endocrine glands, or of changes in the renal tubular cells themselves (fig. 3, *c*, *d*, *e*). Evidence has been presented above for humoral factors which influence tubular transfers of water and electrolytes in congestive heart failure. If adrenal steroids are involved, their secretion requires a stimulatory mechanism, whether the pathway goes from the sympathetic nervous system through the secretion of epinephrine to the production of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland, or whether the latter receives its stimulus from the central nervous system via the hypothalamus. In either case a receptor tissue (fig. 3, *d*) is probably stimulated in the normal subject by changes in the distribution of its water and electrolytes; in the subject with congestive failure the response may be altered by metabolic changes in the receptor tissue or by stimuli of a different nature, perhaps associated with stress. Antidiuretic hormone production by the posterior pituitary is initiated not only by central nervous system stimuli but by certain hypothalamic osmoreceptors as well (fig. 3, *e*).[71] This is a clear example of fluid distribution in a remote tissue modifying renal function. The functions of these osmoreceptors and how they may be involved in congestive failure, at least under certain circumstances of therapy, are discussed below. Finally, in the light of present knowledge one can believe that renal tubular transfers are conditioned by factors present in the renal tubular cells themselves (fig. 3, *c*). These cells may share with those of peripheral tissues changes in volume and electrolyte composition resulting from altered metabolic processes. That such is the case in congestive failure, however, has not been demonstrated.

The physiologic regulation of intake of water and electrolytes (thirst and appetite) is probably effected through certain tissue factors, such as cellular hydration (fig. 3, *f*). These regulating mechanisms appear to function in an abnormal way in congestive failure since the normal relationships of intake to output are maladjusted during the period of edema formation. Such may also be the case following prolonged administration of mercurial diuretics (see below).

Secondary changes in the peripheral tissues (muscle) may directly alter the exchange between cells in these tissues and the immediate internal environment, the interstitial fluid (fig. 3, *b*). Evidence has been presented that transfers of water into and out of cells may be effected without any primary change in extracellular tonicity and without any net transfer of solutes across the cell boundary, that is, by changes in effective osmolar concentration of the solutes within the cell. This evidence is of several kinds. In intact man and animals it has been shown experimentally[72, 73] that significant discrepancies may exist between the total water balance and the total sodium plus potassium balance of the body, discrepancies that, in the opinion of the authors, could only be explained by changes in the osmotic activity of solutes within the intracellular phase. In another type of experiment based on direct analysis of skeletal muscle before and after certain manipulations of extracellular fluid, a similar discrepancy was found between the observed transfers of water and those predicted from the transfers of base.[74, 75] Other workers[76] have observed phenomena that are most easily explained by such a process. Presumably such a change in the osmotic activity of intracellular solutes is due to changes in the degree of dissociation of molecular aggregates. Such changes are most likely conditioned by metabolic processes. Hill[77] has demonstrated that following stimulation of a frog's muscle, under anaerobic conditions, there is an increase in its total effective osmolar concentration and when oxygen is introduced into this system, the total osmolar concentration returns to its previous level. More recently, Robinson[78] has found that transfers of water in slices of rat kidney cortex are dependent upon oxygenation. The "active process" of water transfer which he postulates is probably the process under discussion. Thus the evidence is strong for the view that metabolic processes not only condition differential exchanges of solutes across the cell boundary,[2] but also changes in osmotic activity of solutes within the cell, and therefore that metabolic processes control the volume of intracellular water.

For these reasons it is not difficult to believe that such a factor as hypoxia, in congestive

failure, might well condition directly the exchanges of fluid in the peripheral tissue (fig. 3, *g*) without a preliminary effect on either intake or renal output of salt and water. The possibility of such an occurrence is suggested by the observations[47] mentioned above which related edema formation to anoxemia. Such transfers of fluid in the peripheral tissue would undoubtedly lead to secondary transfers elsewhere in the body but this fact should not detract attention from the possibility that the first transfer took place in the periphery.

Therapeutic measures in congestive failure may further modify the primary and secondary relationships listed in table 1; this is especially true of the prolonged use of mercurial diuretics. The

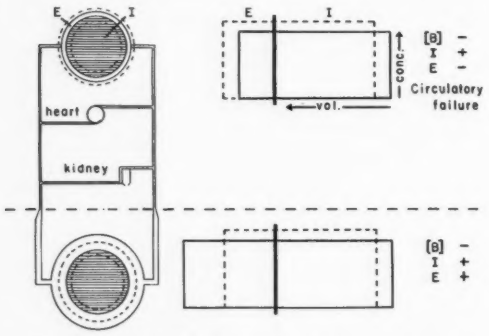

FIG. 4. Diagram of "systemic" dehydration in the presence of edema: regional differences in distribution of body fluids.

already complex relationships of the physiologic and chemical factors in congestive failure may be further complicated by at least one therapeutic agent. Since mercury is an enzymatic poison because of its ability to combine with sulfhydryl groups, it is reasonable to look for its effects in congestive failure at the cellular level, that is, among the *secondary relationships* in table 1. The problem posed by the hyponatremic mercury-fast patient in congestive failure exemplifies the extreme complexity of the relationships of the physiologic factors involved. The remainder of the discussion is devoted to a consideration of this special aspect of congestive failure.

"Systemic" sodium depletion following prolonged mercurial therapy (the low-salt syndrome) may augment the circulatory and renal failure. Changes in composition of extracellular fluid with further deleterious effects in the circulation have been recognized for some time to occur in the presence of prolonged administration of mercurial diuretics. Klinghoffer[79] described in four such patients the occurrence of hemoconcentration and azotemia. These findings suggested a contraction of plasma volume and an increased degree of renal insufficiency which probably was the result of a further drop in renal blood flow. Schroeder[44] has reported a series of patients with similar findings and with hypochloremia and hyponatremia, who responded to the administration of hypertonic solutions of sodium chloride. This condition in cardiacs he has designated as the "low-salt syndrome." Presumably these patients have a "systemic" sodium depletion and dehydration in the presence of localized or regional edema. It is easily understood how this paradoxic situation can occur. During the administration of mercury which inhibits the tubular reabsorption of sodium, salt is lost from the only portion of the body fluids immediately available to the kidney, namely, the plasma flowing through it. If the circulation is adequate, edema fluid may be mobilized to replace the salt and water deficits of the circulating plasma, and diuresis ensues. If, however, for such reasons as impaired cardiac action, increased hydrostatic pressure due to gravity, hypoalbuminemia, that is, "prerenal deviation," the circulation is not able to effect a mass movement of fluid from the segregated pools of edema, then the rest of the "systemic" extracellular fluid is depleted, with further circulatory collapse instituting a vicious cycle. The results of this sequence of events are represented diagrammatically in figure 4.

The hyponatremia of the low-salt syndrome should produce, in sequence: (1) intracellular overhydration; (2) inhibition of antidiuretic hormone production (through Verney's osmoreceptors) and inhibition of thirst; and (3) diuresis. The hyponatremia described as a cardinal sign of the low-salt syndrome implies a state of intracellular overhydration. This is a condition which in normal subjects is associated with inhibition of the antidiuretic hormone (ADH)

of the posterior pituitary and diuresis.[71] It is pertinent, therefore, to speculate as to how the intracellular fluid may be altered in these circumstances and how such alteration might in turn affect the circulation and renal function.

Evidence is presented in the papers which are to follow that hyponatremia frequently occurs in patients with congestive failure and that it is usually associated with the administration of mercurial diuretics. In addition it is not always associated with the "low-salt syndrome" insofar as the latter is indicated by a successful response to hypertonic sodium solutions. If the removal of sodium from some portion of the body is not the major factor, some other mechanism must be invoked to account for the maintenance of a low concentration of sodium and total electrolyte in the body fluids in the presence of edema.

The osmoreceptors of the posterior pituitary, as described by Verney,[71] represent one intracellular fluid in which changes of composition may materially affect the distribution of fluids throughout the body (fig. 3, *e*). When Verney injected in the area of the supraoptic nuclei hypertonic solutions of substances which did not readily cross the cell membrane, the diuresis of a standard water load was inhibited. He postulated that the osmotic effect of these solutions on the "osmoreceptor" cells is to reduce intracellular fluid volume with a consequent stimulation of the antidiuretic hormone production by the posterior pituitary. The antidiuretic hormone as a humoral agent then increases the reabsorption of water in the distal tubule of the kidney. If thirst is directly related to intracellular hydration,[48, 80, 81] wherever the receptor of this stimulus is located, the effect of sodium loading on thirst and on antidiuretic hormone production may be represented diagrammatically as in figure 5*A*. The converse, the effect of water loading, has not been experimentally demonstrated by Verney, but for purposes of discussion may be assumed to hold true: intracellular overhydration results in inhibition of antidiuretic hormone production, and abolition of thirst (fig. 5*B*). According to this theory, cellular overhydration as the result of sodium depletion should also inhibit antidiuretic hormone production and abolish thirst (fig. 5*C*). In our previous experiments on sodium depletion,[62] it was found that the abolition of thirst did occur, but diuresis did not occur, apparently because of failure of the general and renal circulation. In the "low-salt syndrome" of systemic sodium depletion, this combination of circumstances should obtain (fig. 4). The administration of hypertonic sodium solution should result in a diuresis of salt and water as the pattern of body fluids moves from that of relative sodium deficit (fig. 5*C*) in the direction of that of sodium excess (fig. 5*A*) provided that improvement of circulatory efficiency occurs before the production of antidiuretic hormone becomes too great.

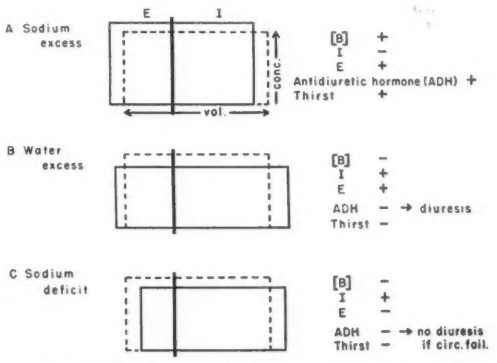

FIG. 5. Diagram of the effects of changes in sodium load and water load on the distribution of water between the phases of body fluid; correlated with the expected effects of antidiuretic hormone production and thirst.

The lack of diuresis and the development of thirst in hyponatremic cardiacs suggests an altered response of cellular receptors which sets the total electrolyte concentration of body fluids at a new level; changes in osmotic activity of cellular solutes might produce such a result. For those edematous patients with hyponatremia who develop thirst but do not have a diuresis following the administration of hypertonic sodium solutions, an alternative mechanism may be hypothesized in the light of the above discussion. As already mentioned, indirect evidence has been presented in the past by ourselves and others[72, 76] for the occurrence of changes in osmotic activity, or osmolarity, of solutes within the intracelluar p hase, changes

which are independent of transfers to and from the extracellular fluid across the phase boundary. If a sufficient amount of intracellular solute, most readily quantitated in terms of the cation or base, were osmotically inactivated, water would pass from the cellular phase. Under these circumstances the total concentration of osmotically active electrolyte would be lowered throughout both phases (fig. 6*A*), *provided the extra water were not excreted from the extracellular phase.* But since the intracellular volume is lowered rather than elevated, production of the antidiuretic hormone should be stimulated and the diuresis inhibited. Thus the

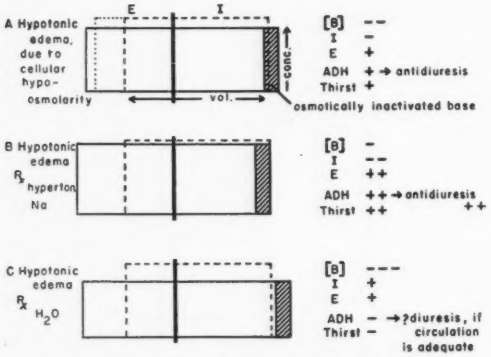

FIG. 6. Diagram of the theoretic effect that inactivation of osmotically active intracellular solutes (or base) would have on the pattern of edema fluids: namely, maintenance of hypotonic body fluids without the usual inhibition by intracellular overhydration of antidiuretic hormone production and thirst; effect on such a situation of treatment with hypertonic sodium solution or with water.

concentrations of sodium and of total electrolyte of the body fluids would be set at a subnormal level in the presence of excess water without the usual stimulus for excretion of the extra water.

If such a process is operative in the hyponatremic cardiac, the results of therapy, at least in part, will depend upon the balance between improvement of the peripheral circulation and production of antidiuretic hormone. If the hyponatremia of an edematous cardiac is due to this mechanism rather than to the renal loss of sodium in excess of water, a different response to the administration of hypertonic sodium solutions would be anticipated. Such therapy should raise the extracellular concentration of electrolyte and cause further intracellular dehydration. If a systemic sodium depletion and vascular collapse is not being rectified, the only result should be increased antidiuretic hormone production and thirst—even at hyponatremic levels (fig. 6*B*). On the other hand, the administration of water or hypotonic sodium solutions would expand the intracellular fluid volume and should so inhibit antidiuretic hormone production (figure 6*C*). This mechanism may be an important factor in the remarkable diureses reported by Schemm[82] to be the result of the administration of water. Schemm has attributed the response to the reduction of an elevated total osmolar concentration within the cell due to nonelectrolyte solutes. This concept is difficult to accept in view of the experimental evidence that solutes, such as urea, which diffuse freely across cell membranes have no effect on either thirst[83] or on antidiuretic hormone production.[71] In any case, the hazard of the pure water treatment would seem to be that, while the intracellular volume is expanded, the tonicity or total electrolyte concentration of the body fluids is further depressed (figure 6*C*). Therefore, if this contributes to "systemic" sodium depletion and associated circulatory insufficiency, the benefit of any inhibition of antidiuretic hormone may be negated by collapse of the circulation.

In summary, it has been pointed out that in congestive failure alterations in fluid distribution in various tissues and organs may result from modification of cellular metabolic processes produced by circulatory dysfunction, and that such alterations may in turn affect secondarily circulatory and renal function. These secondary factors may be effective locally in the myocardium, the cells of the peripheral vascular system, the cells of the renal tubule, or the cells of peripheral tissues; they may condition intake and output of water and electrolytes through humoral mechanisms dependent upon stimuli in such tissues as the receptors of the anterior pituitary-adrenal cortex axis or in the osmoreceptors of the posterior pituitary gland. These secondary factors appear to be modified further by the therapeutic adminis

tration of mercury over long periods of time which may affect both peripheral and renal circulation and the "setting" of the osmoreceptors.

Summary and Conclusions

In this discussion an attempt has been made to review some of the factors which enter into the chain of events leading from cardiac and circulatory dysfunction to the congestive state. The relationship of circulatory to renal factors has been discussed; abnormalities of tubular as well as of glomerular function suggest that endocrine and possibly other factors are involved in the sequence. In short, the homeostatic mechanisms which control body fluid volume, unknown in part, may be functioning in an abnormal way in congestive failure.

This consideration directs attention to the relationships of the state of fluid distribution in various tissues to the circulation and kidneys. Evidence has been found that intracellular as well as extracellular fluid abnormalities exist in congestive failure. Since such abnormalities certainly modify circulatory and renal function in other conditions, it is reasonable to consider that they do so in the edematous patient. There are various tissues and cells in which these secondary mechanisms may be initiated, given a primary disturbance in cellular metabolism which is related to circulatory dysfunction. Fluid transfers may be affected directly by changes in the myocardium, the renal tubular cells, and the peripheral tissues, and indirectly through hormonal mechanisms by changes in the receptor cells of the adrenal cortex or the osmoreceptors of the posterior pituitary.

Changes in cellular hydration may be related to altered metabolic processes influencing the transfers of electrolytes and the osmotic activity of the solutes within the cells. Such changes occurring in the osmoreceptors of the posterior pituitary would affect antidiuretic hormone production, and possibly the sensation of thirst. At least following the prolonged administration of mercurial diuretics, some such mechanism appears to set a new level of total electrolyte in body water.

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The Distribution of Body Fluids In Congestive Heart Failure

II. Abnormalities in Serum Electrolyte Concentration and in Acid-Base Equilibrium

By R. D. Squires, M.D., R. B. Singer, M.D., G. R. Moffitt, Jr., M.D., and J. R. Elkinton, M.D.

The distribution of values of serum concentrations of sodium, chloride, potassium, and total carbon dioxide were studied in a large group of patients with congestive heart failure, and compared with the values in a smaller group of normal subjects used as controls. The depression of sodium and chloride concentration, and the elevation of total carbon dioxide content were evaluated in terms of renal function and mercurial therapy. In 11 of the cases with high serum contents of total carbon dioxide the acid-base equilibrium was precisely defined by measurement of pH in cutaneous whole blood and calculation of the pressure of carbon dioxide and of the concentration of buffer base.

THE PLASMA or serum of blood is the most readily sampled portion of the body fluids. It would therefore seem logical to begin an investigation of disturbances in distribution of water and electrolytes in any clinical condition by observing the concentration of some of the principal electrolytes in plasma or serum. Such a survey in patients with congestive heart failure is the subject of this report, and is the first step in a study of some of the problems outlined in the preceding paper.[1]

Experimental Material

Fifty-four samples of serum from 44 patients with congestive heart failure were analyzed for sodium, chloride, carbon dioxide, and potassium. Multiple samples in the same patient were obtained, with two exceptions, on different admissions to the hospital; in the two exceptions, the second sample was obtained after a therapeutic regime of many days not involving the use of sodium solutions. The patients were selected only insofar as they were patients with clinical heart disease associated with predominantly peripheral edema*; patients with pulmonary edema only were not included. Likewise, patients with right heart failure and edema which was secondary to primary pulmonary disease (cor pulmonale) were excluded from the series. This was done to obviate the effects of primary pulmonary dysfunction on carbon dioxide elimination and hence on the acid-base balance.

The etiologies of the heart disease in the group, in order of decreasing frequency, were as follows: chronic rheumatic heart disease, 16; hypertensive heart disease, 15; arteriosclerotic heart disease, seven; syphilitic heart disease, two; constrictive pericarditis, two; active rheumatic myocarditis, one; and congenital heart disease, one. No attempt is made to present

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* The cardiac patients studied in this and in the following papers had clinical evidence of congestive failure; that is, increased venous pressure as shown by jugular distention or by direct measurement, as well as by peripheral edema.

the serum concentrations of electrolytes according to organic etiology of the heart disease since no particular correlations were apparent on preliminary analysis.

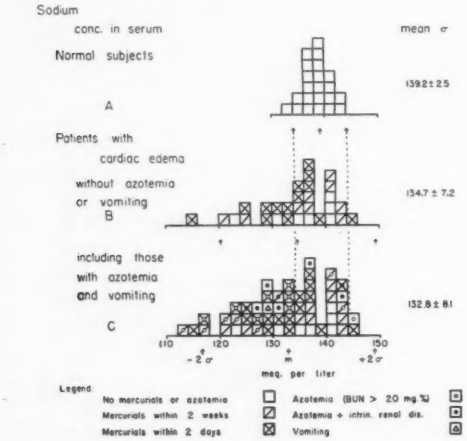

FIG. 1. The distribution of serum concentrations of sodium in normal subjects and in patients with "cardiac edema," that is, congestive heart failure.

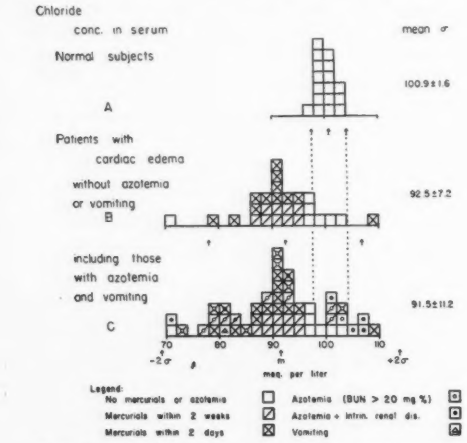

FIG. 2. The distribution of serum concentrations of chloride in normal subjects and in patients with "cardiac edema."

In the presentation of the data as curves of distribution of each electrolyte concentration considered (figs. 1 to 4), the observations are labeled according to certain pathologic variables or conditions that seemed most likely to affect the phenomena being analyzed. The symbols for these variables are designated in the legend of each figure and were assigned according to the following criteria. Patients who had received *mercurial diuretics* are scored according to whether the last dose had been given

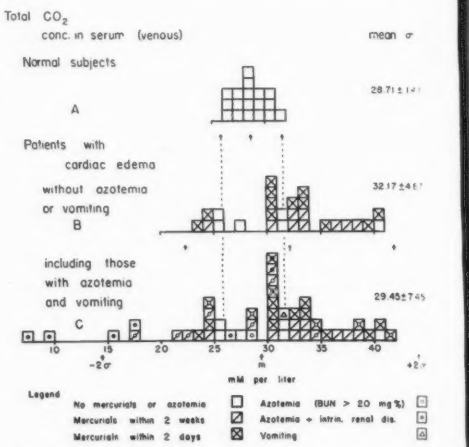

FIG. 3. The distribution of serum contents of total carbon dioxide in normal subjects and in patients with "cardiac edema."

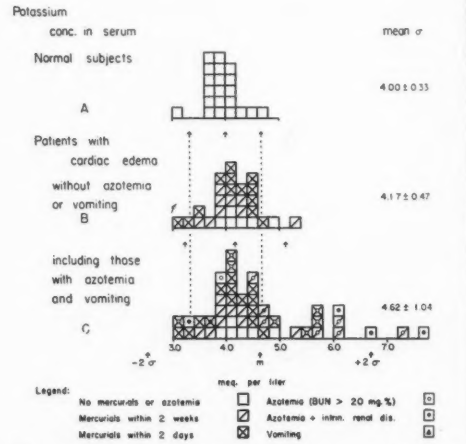

FIG. 4. The distribution of serum concentrations of potassium in normal subjects and in patients with "cardiac edema."

within two days or two weeks of the time the serum analysis was made; no indication is given of the duration or frequency of mercurial therapy. All of the patients had been, and were, on low sodium diets. Patients with *renal insufficiency* were arbitrarily separated from the others by the presence of azotemia as in-

dicated by a blood urea nitrogen content of more than 20 mg. per 100 cc. These patients were then subdivided into those who did or did not have intrinsic renal disease, according to the history, physical examination for evidence of extensive vascular damage and hypertension, and laboratory findings. One patient who had lost gastrointestinal fluids by *vomiting or diarrhea* within one week of the time of study was so designated.

Eleven of the patients were selected for detailed blood studies of their acid-base balance. These patients were mainly from those who had exhibited an elevation in the total carbon dioxide content of venous serum.

In 19 of the patients extensive studies were made of the internal and external transfers of water and electrolytes, by the balance technic. These studies are presented in the subsequent communications.[2, 3]

Serum concentrations of electrolytes were determined in 21 control subjects for purposes of comparison with the patients with congestive heart failure. These control subjects were healthy, active young adult male and female technicians, nurses, and physicians.

Chemical Methods

Sodium and potassium in serum were determined by use of a Barclay internal standard flame photometer.[4] In our hands[4] the standard deviation (σ) about the mean of duplicates was for sodium, ± 0.75 per cent, and for potassium, ± 1.36 per cent. Significant differences, therefore, are those that are greater than $\pm 2\sigma$, or approximately ± 2.1 mEq. per liter of sodium and ± 0.11 mEq. per liter of potassium.

Chloride was measured by the method of Eisenman[5] and the total carbon dioxide content of serum by the method of Van Slyke and Stadie.[6] The acid-base equilibrium of cutaneous whole blood was determined by the microtechnic of Shock and Hastings.[7] From the pH, total carbon dioxide content, and hematocrit values were calculated the pressure of carbon dioxide (pCO_2) and the concentration of buffer base ([BB]) according to the nomogram of Singer and Hastings.[8]

Results

The results of the study are presented in figures 1 to 5 and in table 1. In the distribution curves in figures 1 to 4, the patients with "cardiac edema," that is, with congestive heart failure, who had no evidence of renal insufficiency or vomiting, are compiled in group B; all the cardiac patients are compiled in group C. The mean values and their standard deviations are listed beside each group. The range of two standard deviations from the mean of the control group A is indicated over the curves of groups B and C by the dotted lines; any individual value in these groups that lies outside this range is taken to have less than a 5 per cent probability of being in the control group ($p = 0.05$).

Sodium. The concentration of sodium in serum was lower than normal in many of the cardiac patients; in only two instances was the level elevated (fig. 1). The mean value in all

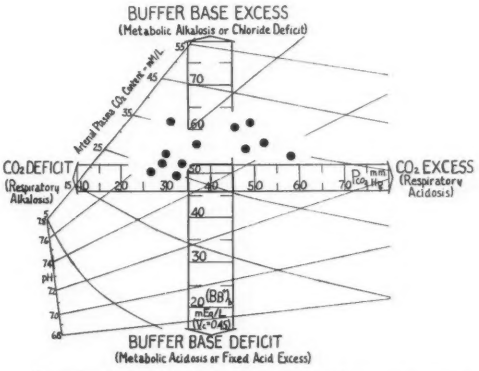

FIG. 5. The acid-base data on 12 edematous cardiacs; the relation of buffer base concentration to carbon dioxide pressure. Presented diagrammatically according to the method of Singer.[34]

the cardiac cases (group C) was 132.8 ± 8.1 mEq. per liter. This is a highly significant difference between the means of these two groups, the p value being < 0.001. The mean value for the cardiac patients without azotemia or vomiting (group B) was 134.7 ± 7.2 mEq. per liter and also differed significantly from the mean of the control group ($p < 0.01$). Within group B only two of the seven cases who had not received mercurials lay outside the normal range. On the other hand, the cases who had received mercurials were distributed over both normal and depressed values.

Chloride. The concentration of chloride in serum was, with one exception, normal or low (fig. 2). The mean value for all the cardiac

cases (group C) was 91.5 ± 11.2 mEq. per liter, compared to the mean for the controls (group A) of 100.9 ± 1.6 mEq. per liter. The mean value for the selected cardiacs (group B) was 92.5 ± 7.2 mEq. per liter. Both of these mean values differed significantly from that of the controls (p <0.01 and <0.001 carbon dioxide in venous serum spread over a wide range of values in all the cardiacs, but tended to be elevated in the selected cardiac patients (group B) (fig. 3). This latter distribution is a reflection of the fact that the concentration of chloride was depressed to an extent greater than that of sodium, and indicates that

TABLE 1. *Analysis of Acid-Base Equilibrium in Blood of Patients with Heart Disease and Congestive Failure, Who Had No Antecedent Vomiting or Alkali Ingestion, and no Recognized Pulmonary Emphysema or Fibrosis*

Patient	Sex	Cardiac diagnosis	Venous serum		Cutaneous whole blood					Acid-base diagnosis
			CO_2	Cl	cell volume	CO_2	pH	pCO_2	buffer base	
			mM. per liter	*mEq. per liter*	*per cent cells*	*mM. per liter*		*mm. Hg*	*mEq. per liter*	
		Normal adult			45	22 ± 2	7.40 ±0.06	41 ± 6	49 ± 3	Range includes about 95% of normal adults
A. W.	M	Constrict. pericard.	26.5	96	42.0	19.5	7.55	27	50	Respiratory alkalosis
E. G.*	M	Hypertensive	28.4	104	56.0	26.0	7.56	29	54	Resp. and sl. metab. alk.
G. B.	F	Chr. rheumatic	32.0	81	41.0	22.9	7.57	30‖	54	Resp. and metab. alkalosis
S. M.	M	Chr. rheumatic	39.5	74	47.0	27.8	7.67	31‖	62	Resp. and metab. alkalosis
J. C.	M	Arteriosclerotic	33.4	95	44.0	20.1	7.47	33	49	Resp. alkalosis
F. P.†	M	Chr. rheumatic	35.1	84	44.5	22.0	7.50	34	52	Resp. and metab. alkalosis
E. S.	F	Hypertensive	33.4	93	42.5	26.0	7.55	37‖	57	Metab. alkalosis
H. H.‡	F	Arteriosclerotic	—	77	42.0	33.3	7.52	46	60	Metab. alkalosis
J. B.	M	Chr. rheumatic	38.6	90	37.0	29.6	7.46	48‖	56	Metab. alk., resp. acidosis
G. C., I§	F	Chr. rheumatic	40.5	80	55.5	29.6	7.49	49‖	62	Metab. alk., resp. acidosis
G. C., II§	F	Chr. rheumatic	37.8	90	54.5	27.2	7.42	52	57	Metab. alk., resp. acidosis
L. D.	F	Hypertensive	33.8	95	37.0	29.3	7.37	58	53	Metab. alk., resp. acidosis

* Lobar pneumonia of left lower lobe and right pyothorax present.

† Pulmonary infarcts found at autopsy.

‡ Bilateral bronchopneumonia present.

§ Pleural effusion.

‖ In these patients, studies of pulmonary function by Comroe[33] did not show the increased residual air capacity and lack of uniformity of alveolar gas mixing which are characteristic of emphysema. In all except patient J. B., the arterial O_2 saturation while breathing room air was low.

respectively). In the cardiacs selected for absence of vomiting and azotemia (group B) six of the seven cases who had not received mercurials were essentially within the normal range, whereas all but one of those who had received mercurials were below the normal range.

Total Carbon Dioxide. The total content of in general the concentration of other undetermined anions was not increased. The mean value for all the cardiac cases (group C) was 29.45 ± 7.45 mM. per liter, compared with a mean for the controls (group A) of 28.71 ± 1.47 mM. per liter. These two values are not significantly different. The mean value for the cardiacs without azotemia or vomiting

(group B), however, was 32.17 ± 4.87 mM. per liter, and differs significantly from the control value ($p < 0.01$). Patients who had not received mercurials, as well as those who had, were distributed within and without the range of control values.

Undetermined Anion Concentration. The difference between the serum concentration of sodium and carbon dioxide plus chloride, used as a measure of undetermined anion concentration, was 9.9 ± 4.7 mEq. per liter for group B compared to 9.5 ± 2.4 for the controls, group A; both of these values are within normal limits of 0 to 11 mEq. per liter.[9] This value for all the cardiacs, group C, was 11.7 ± 6.4, and is slightly higher than the control group because of the presence of renal insufficiency. These data are not presented graphically.

Potassium. The concentration of potassium in serum was, with few exceptions, normal or elevated (fig. 4). The mean value for all the cardiacs (group C) was 4.62 ± 1.04 mEq. per liter compared with a control mean (group A) of 4.00 ± 0.33 mEq. per liter. The mean for the selected cardiacs (group B) was 4.17 ± 0.47 mEq. per liter, and does not differ significantly from the control group. In group B very few of those cases who had, or who had not, received mercurials lay outside the range of control values.

Acid-Base Equilibrium. The data on 11 selected patients are given in table 1, and are presented graphically in figure 5. Most of these patients had elevated concentrations of total carbon dioxide in venous serum. In nine of the 12 studies the pH of cutaneous blood was elevated (above 7.46). The values for the partial pressure of carbon dioxide and buffer base were calculated to evaluate the respiratory and metabolic factors involved in the acid-base disturbance. If the normal range of carbon dioxide pressure in cutaneous blood is taken to be 35 to 47 mm., six of the 12 samples show an abnormally low carbon dioxide pressure, or a carbon dioxide deficit resulting from hyperventilation, and four show an abnormally high carbon dioxide pressure or carbon dioxide retention. The values of whole blood buffer base concentration are in the normal range of 46 to 52 mEq. per liter (normal for a red cell volume of 45 per cent) in only two cases; in the remaining ten there is an excess of buffer base, or metabolic alkalosis. The co-existence of carbon dioxide deficit and buffer base excess in four of the patients indicates that both the respiratory and metabolic factors have undergone a primary disturbance, which can be called a "mixed alkalosis." In the three samples characterized by carbon dioxide *retention* and buffer base excess it is impossible to state with certainty whether both disturbances are primary or whether one is secondary to the other (compensatory elevation of the buffer base in response to primary carbon dioxide retention, or vice versa).

Interpretation of Results

The interpretation of the results of these serum and blood studies depends to a large extent on the clinical evaluation of the patients and on the balance data obtained during treatment of some of them. Although the latter are to be presented subsequently, certain statements appear justified from the results just detailed.

Serum sodium concentration was definitely lowered in many of these cardiacs and for the group as a whole, even when those with vomiting or renal insufficiency were excluded. Thus these two latter conditions, while augmenting the hyponatremia, do not account for it. On the other hand, six of the seven patients who had received no mercurial diuretics had serum sodium levels within the normal range. The inference is clear that the mercurial therapy was directly related to the hyponatremia. Unfortunately, the paucity of cardiacs who had not received mercurial diuretics prevents subjecting this inference to a statistical analysis. But it would appear that, at least in the edematous cardiac who has received mercury, hyponatremia is a common finding. No index of frequency, as opposed to recency, of mercurial injection is available in this study. Yet this may be the more significant factor of the two since neither patient F. J. in the succeeding study[2] nor the subjects observed by Blumgart and his co-workers[10] developed hyponatremia during massive diuresis resulting from a single dose of mercurial drug. Whatever the effective factors may be in respect to mercurial

administration, such hyponatremia must be due to deficit of sodium (and total electrolyte in the body fluid) relative to water even though the total quantities of both of these substances in the body are in excess of normal. Whether this hypotonicity of the body fluids is due to loss of salt relative to water, or to retention of water relative to salt, cannot be stated from the data presented above. The known effect of mercury on the renal excretion of salt suggests the former explanation; the observation in patients reported in the succeeding paper[3] of falling serum sodium levels when the sodium balance was in equilibrium or positive, suggests the latter explanation, that is, that water retention at least in part is responsible for the hyponatremia.

The *serum chloride concentration* was depressed to a greater extent than that of sodium, and the *carbon dioxide content* was elevated. This fact can hardly be explained by a primary effect of mercury on sodium excretion or by a retention of water. In the absence of renal failure and vomiting, the following possible explanations may be considered. (1) In mercurial diuresis in edematous patients chloride and sodium are excreted in approximately equivalent amounts, and therefore more chloride than sodium is lost relative to the usual proportions of sodium to chloride of 1.3 to 1.0 in extracellular fluid. The net effect of such losses of water, chloride, and sodium would be a fall in the concentration of chloride relative to sodium. This explanation of the hypochloremic alkalosis seems valid in view of the data presented in the next paper.[2] (2) Chloride is excreted and the bicarbonate concentration of extracellular fluid thereby elevated, as a secondary response to a primary respiratory retention of carbon dioxide. The presence of a low carbon dioxide pressure in blood in a significant number of cases renders this explanation invalid for those cases and unlikely for the group as a whole. (3) Chloride is displaced by other undetermined anions. This is not a usual physiologic adjustment since bicarbonate ion (HCO_3^-) is usually displaced under these circumstances; the absence of a significant increase in group B over group A in the difference between the serum concentrations of sodium and carbon dioxide plus chloride makes this explanation untenable. (4) A metabolic alkalosis with hypochloremia was present as a result of intracellular potassium deficiency (according to the theory of Darrow[11]). This possibility cannot be ruled out by the data above, and, as will be seen in the subsequent paper, many cardiacs retain potassium when administered and, therefore, are probably deficient in the ion.[2, 3] However, the absence of hypokalemia in these cases and the failure to maintain the normal concentration of chloride and carbon dioxide following potassium therapy, do not support this hypothesis.

The *respiratory alkalosis* indicated by the low carbon dioxide pressure calculated in some of the patients is the result of some stimulus or stimuli to the respiratory center other than a metabolic acidosis, since the latter was not present in the group without renal insufficiency. These stimuli cannot be identified completely from these data; presumably they are reflexes from the congested lung and/or anoxemia such as was found to be present in two of these cases (table 1). Respiratory retention of carbon dioxide (*respiratory acidosis*) was present in some of the cases. This may have been due primarily to poor ventilation of the alveoli although no clinical or functional evidences of permanent lung changes, notably emphysema and fibrosis, could be adduced in the particular cases in which the carbon dioxide pressure was elevated (table 1). In patient G. C. (I), who was anoxemic, the presence of pleural effusion and possibly pulmonary congestion may have interfered with the excretion of carbon dioxide. Patient J. B. was not anoxemic and had no functional evidence of emphysema (table 1). It is possible that in this patient and in patient L. D. the respiratory retention of carbon dioxide was a secondary and compensatory response to the metabolic alkalosis which was so frequently present, although such a response seldom occurs to any great magnitude.[12]

Discussion

These findings were not entirely unexpected. Although Blumgart and his associates[10] found the serum concentration of sodium and chloride to be essentially unchanged after mercurial diuresis, others have found the concentration of these ions to be lowered.[13–16] Similar observa-

tions have led to use of the term "low-salt syndrome" to describe the edematous patient who has become refractory to mercurial diuretics and who usually has a lowered concentration of sodium and of chloride in serum.[17, 18] The physiologic mechanism by which this state is induced and its therapeutic implications are discussed in a subsequent paper.[3] It appears to the authors that hyponatremia in cardiacs who have been receiving mercurials is more frequent than the low salt syndrome. This is true insofar as that syndrome is identified by a response to hypertonic sodium solutions in terms of improvement of the circulation, improvement of renal function, and diuresis of the edema. It is possible, therefore, that in some of the patients the hyponatremia represents the setting of a new level of total electrolyte concentration in body fluids, possibly by changes in cellular osmolarity, rather than by a systemic depletion of sodium.[1, 3] But whatever may be the mechanism involved, hyponatremia and hypochloremia appear to be frequent sequelae of mercurial therapy.

Hypernatremia, on the other hand, was conspicuously absent in this group of patients. Peters[19] has suggested that the renal abnormality in respect to sodium excretion in the cardiac is a mistaken "dehydration reaction," that is, an increased tubular reabsorption of sodium and chloride under conditions of water deprivation and rising concentration of sodium and chloride in serum.[20] Presumably such a response would tend to result in a slightly elevated concentration of sodium in serum. Unfortunately these data cast no light on this problem because of the insignificant number of determinations of serum sodium concentration in patients with congestive heart failure who had received *no* mercurial diuretics during the preceding two weeks. Sodium chloride may have been retained in excess of or to an equivalent degree to water in the initial stages of the disease in these patients. But at the time these observations were made, almost always following mercurial therapy, the hyponatremia in the presence of edema can only mean that the excess of water exceeded that of salt.

The elevation of the concentration of serum bicarbonate in association with hypochloremia has been reported in cardiacs in the past.[10, 21, 22] Peters, Bulger, and Eisenman[23] interpreted this finding as indicating a secondary response to a primary pulmonary retention of carbon dioxide similar to that found in patients with emphysema and pulmonary fibrosis. Many of their patients had extensive pulmonary disease, but unfortunately no measurements of pH were recorded; it is not possible, therefore, to ascertain whether or not the carbon dioxide pressure was sufficiently elevated to confirm this interpretation. Winkler and Crankshaw[22] interpreted in a similar manner the data which they obtained on a patient with congestive heart failure. Such a secondary response to a primary carbon dioxide retention in patients with heart failure usually has been thought to be restricted to those patients who also had extensive structural changes in the lungs, namely, emphysema and fibrosis. Our data indicate that an elevated serum bicarbonate concentration and hypochloremia frequently are not secondary responses to carbon dioxide retention occurring in those cardiacs who have extensive pulmonary disease. In only three of the 12 patients in whom a detailed study of the acid-base equilibrium was made, was there evidence of a pulmonary lesion other than passive congestion. And in at least one-half of the 12 patients the conjunction of a *lowered carbon dioxide pressure* with elevated buffer base rules out the latter as being a compensatory response to respiratory retention of carbon dioxide. A carbon dioxide deficit (or respiratory alkalosis due to a diminished carbon dioxide pressure in the alveoli) has been described[24–26] and may be explained as the result of an anoxemia or abnormal pulmonary reflex stimulus to hyperventilation, but the compensatory renal response should be a retention of chloride, with a reduction of the buffer base, or a secondary metabolic acidosis. The metabolic alkalosis in these cases and in those in which the carbon dioxide pressure was normal, cannot be explained as a secondary or compensatory response to a primary retention of carbon dioxide by the lungs.

It is not unreasonable to inquire whether the metabolic alkalosis found in some of these patients may not be related to disturbances in intracellular electrolyte content, since evidence is presented in the following papers that disturbances of intracellular fluid do occur in pa-

tients with edema and heart failure. Darrow and co-workers have shown that in the rat under conditions of the steady state of uninterrupted renal function, the experimental production of intracellular potassium deficiency and sodium excess results in a metabolic alkalosis.[11] In patients showing this phenomenon the renal threshold for chloride is low.[27] Although many of these cardiacs have been shown in the balance studies[2, 3] to retain potassium when administered, the deficiency of the ion, if it existed, was not sufficiently great to result in a lowering of the potassium concentration in the serum and extracellular fluid, nor was the uptake of potassium always associated with the restoration to normal of the bicarbonate level. Thus, a relationship between intracellular electrolyte disturbances and the metabolic alkalosis seems unlikely, but is not entirely ruled out, since it is known that the extracellular concentration of potassium does not always mirror the state of cellular stores of the ion,[28] and since the extracellular alkalosis may be more directly related to changes in intracellular sodium than potassium.[27]

In view of these facts and of the frequent finding of normal or low values for carbon dioxide pressure (pCO_2) in many of these patients, the most likely explanation of the metabolic alkalosis as defined by the elevated buffer base values, is that under the influence of mercurial therapy and diuresis, chloride is excreted in greater amounts than sodium relative to their proportional contents in extracellular fluid. This phenomenon has been recorded by other workers[10, 29–31] and was observed in the patients reported in the next paper.[2] The acid-base disturbance in any given cardiac patient would appear to be compounded of a variety of factors: respiratory stimuli (central and peripheral), pathologic changes in pulmonary structure, prior treatment with salt and diuretics, and possibly intracellular electrolyte abnormalities.

Summary and Conclusions

The serum concentrations of certain electrolytes were studied in 54 samples from 44 patients with peripheral edema due to congestive heart failure. The patients without renal insufficiency are presented in group B and all of the patients are grouped together in group C. Most of the patients had had mercurial diuretics within two weeks of the time of sampling. The results are compared to values obtained from a control series of normal subjects, group A.

The mean concentration of serum sodium was significantly lower in groups B and C. The mean concentration of serum chloride was depressed to a greater extent than was that of sodium, in both groups B and C. The mean content of carbon dioxide was elevated in group B only. The mean concentration of serum potassium was not altered significantly in either group.

In 12 studies of acid-base equilibrium in 11 patients, nine cases were found to have an elevated buffer base concentration. Six of these were cases of primary metabolic alkalosis; and in four of these six, the carbon dioxide pressure was low, indicating the coexistence of a primary respiratory alkalosis. In three of the cases with an elevated buffer base concentration this change might have been secondary to the high carbon dioxide pressure (primary carbon dioxide retention or respiratory acidosis). The remaining two cases had a normal buffer base concentration but had a low carbon dioxide pressure (primary carbon dioxide deficit or respiratory alkalosis).

It is concluded: (1) that hyponatremia and hypochloremia are common findings in edematous cardiacs who have received mercurial diuretics; (2) that the relatively greater degrees of hypochloremia and the elevated bicarbonate concentration (the metabolic alkalosis) frequently found, (a) usually are not explicable as a secondary response to a primary carbon dioxide retention, but (b) are probably due to excretion of chloride in relatively greater amounts than of sodium during mercurial therapy and diuresis.

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Regional Vasomotor Tone in Normotensive and Hypertensive Dogs

By ARNOLD H. WILLIAMS, M.D., AND HENRY A. SCHROEDER, M.D.

A new method for estimating vasomotor tone in a local circulation by means of the asystolic arterial pressure gradient was applied to the renal, femoral, brachial, and mesenteric vascular beds of normal dogs and of dogs made hypertensive by various technics. The splanchnic circulation apparently contributes the greatest proportion of the increase of resistance in anesthetized hypertensive animals. The correlation of vasomotor tone with diastolic pressure was good only in the mesenteric area. Some differences in these four areas were found between renal and neurogenic hypertension.

FOR many years it has been known that "essential" hypertension is due to an increase of total peripheral resistance.[1]* Opinion diverges, however, about the location of the changes of vasomotor tone, some studies indicating that the increase is uniform throughout the body,[1,6-8] others suggesting that regional differences occur.[9-11] Possibly the regional differences depend upon the type[12] of hypertension studied. Since in some ways the varieties of experimental hypertension are similar to those of "essential" hypertension,[13] patterns of regional vasomotor tone in the former should furnish some insight into the nature of the conditions. This study is concerned with establishing these patterns.

Because the usual approach[2] to the estimation of regional vasomotor tone is both awkward and difficult, a new method was developed. The asystolic arterial pressure gradient, defined as the descending curve of intra-arterial pressure following occlusion of an artery supplying a local circulation, can be used to measure regional peripheral resistance. The measure is quantitative when collateral circulation is excluded and qualitative in the presence of collateral circulation.[14] Although changes in the curves parallel changes of vasomotor tone, only one function of the gradient is directly applicable to the measurement of tone, namely, the level of intra-arterial pressure six seconds after arterial occlusion or EP_6.[15] Because the value of EP_6 is relatively unaffected by systemic blood pressure, intra-arterial blood volume, or the rate of local flow, it provides an index of regional vasomotor tone. From such a value a crude approximation of the actual degree of constriction may be made in certain areas.[16]

The present report concerns measurements of regional vasomotor tone in four vascular

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* Because considerable semantic confusion exists in writings on peripheral resistance, the following terminology was adopted and used throughout this report. The ratio, pressure: flow, sometimes called resistance,[2] is used as such. The term *resistance* per se indicates the *force* or *hindrance*[3] acting to prevent the escape of blood from a local circulation, both that produced by the size of the arteriolar outlet and that resulting from the effects of the viscosity of blood. This factor corresponds to Pappenheimer's definition of "resistance proximal to the effective mid-point of the capillary."[4] Total peripheral resistance (TPR) indicates the total *force* acting to prevent the escape of blood from the arterial system. The contribution of a given vascular bed to total peripheral resistance is equivalent to the reciprocal of its resistance and herein is designated *conductance*.[2] The size of the arteriolar outlet, the arteriolar diameter, and total cross sectional area of the arterioles are used as synonyms for *vasomotor tone*.[5] The term *degree of vasoconstriction* indicates the actual amount by which the arterioles are constricted.

For the purposes of this discussion the following factors are not included: the inertia of the mass of flowing blood, "postcapillary resistance" or the force opposing flow through venous circulation,[4] and the frictional force exerted by the large vessels.

areas of anesthetized dogs, both those with normal blood pressure and those with various types of hypertension. Evidence is presented that, of these areas, the mesenteric is most intimately concerned with the regulation of diastolic blood pressure. Although hypertension of the neurogenic variety has been ascribed to changes of cardiac output alone[17, 18] vasoconstriction is present. The pattern of regional vasomotor tone in renal hypertension differs but mesenteric constriction is also marked.

Methods

Asystolic arterial pressure gradients were obtained in four major arterial beds of dogs anesthetized with pentobarbital, 0.02 Gm. per Kg. intravenously. Forty-three normal animals were used, determinations being made in the femoral region of 24 dogs, the brachial of 17, the renal of 22, and the superior mesenteric of 18 according to methods previously described.[14] Usually measurements were taken in two areas, occasionally in four. Several determinations were made in each region and the order of procedure from one area to the next was varied intentionally. With few exceptions the effects of collateral flow were only noticed in the limbs. Collateral circulation was excluded from the brachial circulation in five instances by tight wire tourniquets[16]; in five others the femoral was isolated similarly.[14] Normally it was minimized by occluding these arteries above the origin of the deep or profundi branches and did not affect the first and second curves obtained.

The blood pressures of the "normal" dogs varied considerably. For purposes of comparison, those with diastolic levels above 110 mm. Hg were arbitrarily classified "spontaneous hypertensive,"[19] those with systolic pressures below 110 mm. as "shock." Hypertension was produced in three ways, a minimal rise of 30 mm. Hg mean pressure being considered significant. Partial constriction of one renal artery caused renal hypertension in 8 dogs,[20] silk perinephritis in one,[21] both methods being supplemented by contralateral nephrectomy. In some instances the affected kidney was explanted beneath the skin.[22] In 4 dogs chronic neurogenic hypertension was engendered by section of the moderator nerves[18] in two stages. Acute neurogenic hypertension was produced in 11 dogs by section of the vagi and ligation of the carotid arteries above and below the sinus. Progressive ligation of the arteries supplying the head induced chronic hypertension in one dog[23]; in 3, normal saline solution was forcibly injected into the cisterna magna to cause the abrupt onset of hypertension.[24]

In each dog asystolic gradients were obtained in two or more of the above mentioned areas. Only those curves which showed no evidence of artefact, collateral circulation, or atypical contour[11] were included. In all instances the intra-arterial pressure six seconds after occlusion (EP_6) was measured to the nearest 2 mm. Hg, changes of ±7 mm. being considered significant.[16]

Results

1. *Regional Values of EP_6* (figs. 1–4)

(a) *Renal.* Normal dogs showed low values of EP_6, their range varying from 4 to 24 mm. Hg (average 16); there was no correlation with levels of arterial pressure. Of 4 dogs in "shock,"

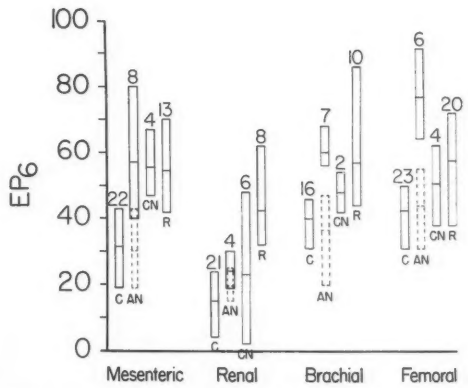

Fig. 1. Regional levels of EP_6 in normotensive and hypertensive dogs. The ends of each open bar represent the extreme, and the central lines the average values of EP_6 (in mm. Hg) obtained in the labeled regional circulations of dogs serving as controls (C), in chronic neurogenic hypertensive (CN) and in chronic renal hypertensive animals (R). The dotted bars represent control levels before the production of acute neurogenic hypertension (AN); the change is indicated by the open bars above. The number at the tip of each bar shows the number of gradient determinations, no more than two in any one area being taken from a single dog.

2 exhibited very low and 2 very high values. In chronic neurogenic hypertension values varied widely (2 to 48 mm.). Acute neurogenic hypertension consistently caused a slight rise (average 5 mm.) (fig. 2). The value of EP_6 quadrupled in the single experiment in which intracranial pressure was increased.

Levels of EP_6 were markedly increased in renal hypertension, being 2 to 4 times normal distal to the Goldblatt clamp. However, renal decapsulation reduced values of EP_6 to high

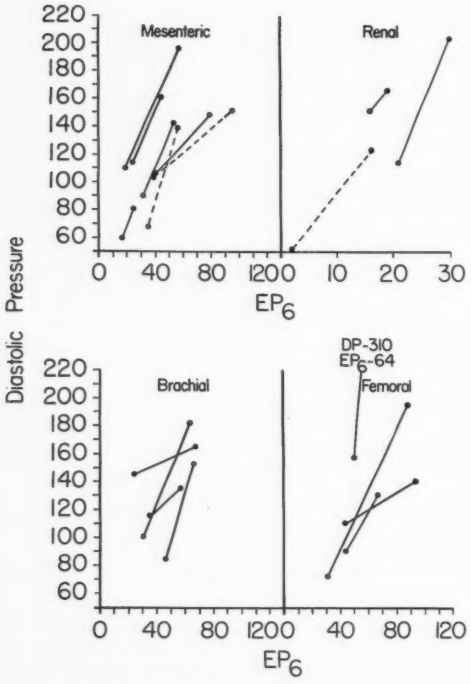

FIG. 2. Effect of acute neurogenic hypertension on regional vasomotor tone. Each diagonal solid line represents the change of tone produced by acute neurogenic hypertension in a single dog. Its lower end shows the control level and the upper end the value after the increase of pressure. Similarly the dotted lines show the changes produced by an acute increase of intracranial pressure. Note that in most instances the slopes of the lines are similar. Both scales are in mm. Hg.

normal values in the 2 hypertensive dogs on which such experiments were made (table 1). In another animal the lumen of the renal artery was obliterated at the site of the clamp, the entire blood supply coming through collateral channels. On the other hand higher values were present in dogs which had had hypertension for less than two months than in those which had the disease for longer periods. EP_6 was also high in the animal with perinephritis (table 1).

(b) *Mesenteric.* Values of EP_6 of normal dogs were remarkably constant in this area (30 to 38 mm. Hg). The variation was greater (19 to 53 mm.), however, in those whose diastolic pressures were higher. Two dogs were in shock, a very low value being found in one and a moderately low value in the other.

Levels were uniformly high in renal and neurogenic hypertension but not in the single dog with cerebral ischemia. In all dogs there was a good correlation between levels of diastolic pressure and EP_6 (fig. 4). Both acute neurogenic hypertension and increased intracranial pressure caused marked increases, averaging 27 mm. and 33 mm. respectively (fig. 2).

(c) *Brachial.* Relatively constant values of EP_6 were found in the brachial circulation of normal dogs (31 to 46 mm. Hg).* They were moderately or markedly elevated in "shock."

Slight to moderate increases were usually seen in renal and neurogenic hypertension, but in 4 Goldblatt dogs the rise was considerable. In acute neurogenic hypertension the average increase was 25 mm.

(d) *Femoral.* In general, the levels of EP_6 in this region (range 31 to 50 mm. Hg) were similar to those found in the brachial circulation. However, high levels of EP_6, comparable to hypertensive values, were found in dogs with elevated diastolic pressures whether or not collateral was excluded. As in the other areas the range of EP_6 was wide in shock.

Of the two highest values obtained, one was in the dog with cerebral ischemia. They were approximately normal in chronic neurogenic but were normal or moderately elevated in

* In this region, as in the femoral bed, the values of EP_6 represent the sum of the effects of vasomotor tone and collateral circulation. The progressive reduction of collateral circulation by the application of tourniquets reduces levels of EP_6.[14] However, when collateral was excluded (with the exception of that passing through bone[16]), values were similar (19 to 52 mm. Hg) to those obtained without exclusion of collateral. It was obvious that the effects of collateral might vary in different animals but it was assumed that these differences were unimportant when series of dogs were compared.

renal hypertension. Acute neurogenic hypertension caused a considerable increase of EP_6, averaging 30 mm. Hg.

2. *Regional Patterns of EP_6 (Table 2)*

(a) *Normotension.* In anesthetized normotensive dogs levels of EP_6 tend to be low in the kidney and mesentery, higher in the limbs (fig. 1).

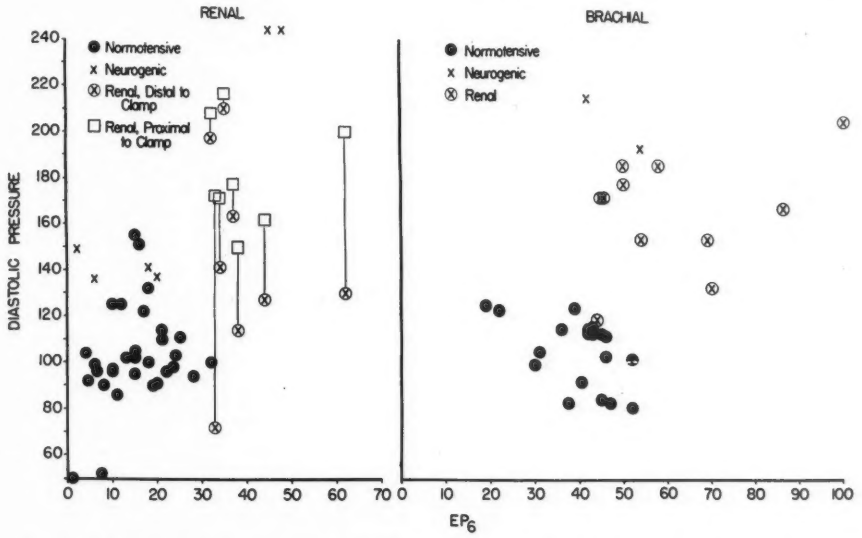

FIG. 3. Relationship of renal and brachial vasomotor tone to levels of diastolic pressure. *Left.* Renal. EP_6 determinations in normotensive, chronic neurogenic and chronic renal hypertensive dogs show a random scatter when plotted in relation to diastolic pressure. The squares indicate levels of diastolic pressure in the femoral artery or in the renal artery proximal to the Goldblatt clamp; the connecting lines to the crosses enclosed in circles indicate the drop of diastolic pressure across the clamp (see table 2). *Right.* Brachial. EP_6 levels in normotensive, chronic neurogenic and chronic renal hypertensive dogs show fair correlation with diastolic pressure in most instances. All scales are in mm. Hg. No more than two values are plotted for any one dog.

(b) *Shock or Hypotension.* Although the number of dogs is small, values of EP_6 varied widely, probably depending upon the state of shock. They ranged from extremely low (1 to 8 mm.) to very high levels (43 mm.) in the kidneys, in the brachial area from normal (30 mm.) to high (52 mm.), in the femoral from low (18 mm.) to high (58 mm.), while those in the mesenteric bed were normal to low (2 to 38 mm.). Many of these values are shown in figures 3 and 4.

(c) *Hypertension.* In chronic neurogenic hypertensive dogs the principal increase of EP_6 was in the mesenteric bed (average 23 mm. Hg), with but slight elevations in the femoral (+5), brachial (+5) and renal (+7) areas (fig. 1). The principal change in chronic renal hypertensive dogs was also in the mesenteric region (average +20 mm. Hg) but levels were higher in other regions (renal, +30 mm. Hg; femoral, +12; brachial, +17). The femoral area was the only one involved in "spontaneous hypertension" (average +18 mm.). A similar situation was seen in the single dog with chronic cerebral ischemia, levels in the femoral bed being +35, but those in the mesenteric area only +5. Gradients were not determined in other areas. Femoral curves were obtained by digital pressure in 3 unanesthetized chronic hypertensive dogs. Value of EP_6 in a renal hypertensive dog was 60 mm., 77 in a neurogenic dog (a very high level), and 37 in a dog with both types of hypertension. Under Pentothal anesthesia the values changed to 46, 85 and 76 mm. respectively. Although the

shapes of the curves were excellent, the method, used in this way, has its obvious limitations.

Comparable increases of EP_6 were found in the femoral (+30 mm.), brachial (+30), and mesenteric (+25) areas in acute neurogenic hypertension. However, only slight changes occurred in the kidney (+5) (figs. 1 and 2). Because of the small number of experiments the changes resulting from an acute increase of intracranial pressure are not clear. Although mesenteric values rose markedly in one instance (+56 mm.) the rise was smaller (+22) in another animal whose blood pressure changed less. In one dog renal values rose from 2 to 16 mm. Hg.

There was a large drop of arterial pressure across the Goldblatt clamp, averaging 92 mm. Hg systolic and 48 diastolic in four dogs (table 1). Pulse pressure distal to the clamp was very small, ranging from 6 to 20 mm. Hg.

3. *Relations of Blood Pressure to Values of EP_6 in Different Regions*

Although there was no obvious relationship between levels of *systolic* pressure and regional values of EP_6, the correlation between levels of *diastolic* pressure of all dogs and EP_6 was good in the mesenteric area,* fairly good in the limbs, but absent in the kidney (figs. 3 and 4).

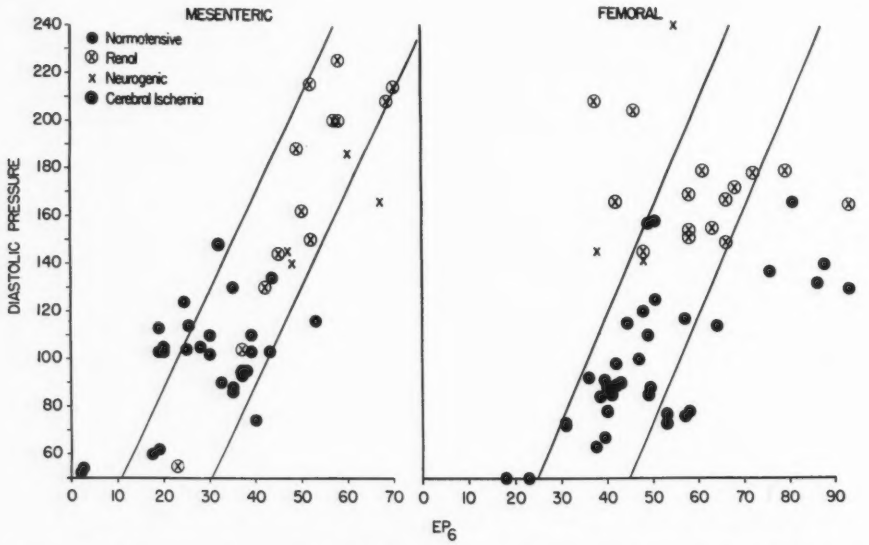

FIG. 4. Relationship of mesenteric and femoral vasomotor tone to levels of diastolic pressure. *Left*. Mesenteric. This figure shows the determinations of EP_6 in the mesenteric vascular beds of normotensive dogs, of animals with chronic neurogenic and chronic renal hypertension, and of the single dog with chronic hypertension due to cerebral ischemia. Note the close correlation of diastolic pressure with EP_6. *Right*. Femoral. EP_6 values in normotensive dogs, chronic neurogenic and chronic renal hypertensive dogs show a fairly good correlation with diastolic pressure at the lower levels. All scales are in mm. Hg. No more than two values are entered for any one dog.

In the kidney, minimal values of EP_6 (av. 9.4 mm.) usually occurred when the pulse pressure was 30 to 40 mm. Hg rather than when it exceeded 40 (EP_6 21 mm.) or was less than 30 (EP_6 20 mm.). However this was not true of neurogenic hypertension. In renal hypertension EP_6 varied inversely as the pulse pressure dis-

* The correlation was with diastolic pressure in the smaller radicles of the mesenteric artery, an area where levels are lower than but presumably proportional to those in the aorta.[25]

TABLE 1.—*The Drop of Blood Pressure across the Goldblatt Clamp and Levels of Renal EP_6 in Chronic Renal Hypertensive Dogs*

Dog No.	Duration of Hypertension (days)	Blood Pressure (mm. Hg)				Blood Pressure Difference (mm. Hg)		EP_6 mm. Hg	% Constricted (r) ‖	Remarks
		Proximal to Clamp		Distal to Clamp						
		Syst.	Dias.	Syst.	Dias.	Syst.	Dias.			
50*	130	310‡	215	271	210	−41§	−5§	35	85.4	
		257‡	204	255	197	−42§	−7§	32	83.8	30 minutes later
56	15	231	183	138	130	−93	−53	62	93.9	
78	260	205‡	145	147	127	−58	−18	44	89.8	
		215‡	145	134	114	−81	−31	38	86.9	10 minutes later
112	90	218	176	156	135	−62	−41	—	—	No flow through renal artery
113†	360	266	177	202	163	−64§	−14§	37	86.2	
		276	171	149	128	−147§	−43§	21§	76.8§	After renal decapsulation
114	220	256	172	78	72	−178	−100	33	84.5	Pressure in small branch of renal artery
		280	188	48	42	−232§	−146§	16§	70.9§	After renal decapsulation, exteriorization of kidney, and ligation of ureteral artery
Averages						92.4	48.6	40.1	87.2	

* Hypertension produced by silk perinephritis.
† Goldblatt clamp on one branch of renal artery and pressures obtained in the other branch.
‡ Femoral arterial pressure.
§ Not included in averages.
‖ See Discussion for method.[16]

TABLE 2.—*Typical Patterns of Vasomotor Tone in Various Vascular Beds*

Dog No.	Type of Hypertension*	Systemic B.P. Syst./Dias. mm. Hg	Mesenteric		Renal		Femoral		Brachial	
			EP_6* mm. Hg	% Constricted (r)	EP_6 mm. Hg	% Constricted† (r)	EP_6 mm. Hg	% Constricted† (r)	EP_6 mm. Hg	% Constricted† (r)
65	Normal	135/104	25	—	14	68.5				
63		125/105			11	63.7			31	68.3
14		140/98			6	54.2	42	74.4		
89	Spontaneous Hypertension	149/124			21	75.9			39	73.1
37		180/134	35	—						
8		178/137					76	86.9		
76	Chronic Neurogenic Hypertension	290/215	48	—	2	40.0			42	74.4
100		>250/244	60	—	48	98.4	55	80.1		
34	Chronic Cerebral Ischemia	197/148	32	—			80.5	87.7		
78	Chronic Renal Hypertension	201/162	50	—	44	89.2	48	77.5	54	80.0
50		310/215	52	—	35	85.5	38	71.7	50	78.7
4	Shock	90/52	2	—	7.5	57.8	40	73.5		
9		96/78					41	73.8	41	73.8
3		86/65			43	88.8	57	81.0		

* See text.
† See Discussion for method.[16]

tal to the clamp but showed no relation to the systemic blood pressure. Values of EP_6 showed no correlation with pulse pressure in other regions.

Discussion

1. *Validity of the Methods*

There is little reason to believe that values of EP_6 do not measure the vasomotor tone of a given region in normotensive and hypertensive states. The asystolic arterial pressure gradient of a local circulation represents the descending curve of intra-arterial pressure and is a function of outflow through the arterioles. Although the initial or α portion of the curve is influenced by (a) the volume of blood in the artery at the time of occlusion, (b) intra-arterial pressure and the elastic recoil of the arterial wall, (c) viscosity of the blood, (d) the number and size of arterioles in the vascular bed, and perhaps, but infrequently, by (e) venous pressure,[14]* EP_6 is but little affected by levels of systemic pressure at a contant degree of tone (± 7 mm. Hg).[16]† With the minimal degree of blood loss characteristic of the present experiments, it is probable that blood viscosity did not vary appreciably; there is no proof that this factor is related etiologically to any type of experimental hypertension.[13]

Unfortunately, because the level of EP_6 is affected by the ratio of intra-arterial volume to the number and size of arterioles in a given region (a factor which differs in each area), one cannot compare the conductance and/or tone of different types of vascular beds by this method, except possibly of the femoral and brachial.[16]‡ For the method to be valid the ratios of EP_6 to resistance must be constant in all regions. With such data as are available[2] these specifications could not be met. Consequently it must be concluded that levels of EP_6 in any region measure vasomotor tone in only that area.

A method was therefore devised whereby the actual degree of constriction might be made comparable in different areas.[16] Renal and brachial pressure-flow curves were plotted against values of EP_6, and arbitrary scales constructed. The brachial scale presumably may be applied to the femoral area.§ However, at best, the method is approximate. The scales are based on extremes of 100 per cent dilatation and 100 per cent constriction, both impossible values in a functioning circulation, and no correction is entered for the effects of blood viscosity[13, 14] or for collateral circulation. The method, although subject to error, provides a useful means for comparing the relative degree of constriction in one local circulation with another.

2. *The Effects of Regional Circulations on Total Peripheral Resistance*

As levels of systolic pressure are primarily regulated by cardiac output, and diastolic pressure, by peripheral resistance,[25] the observed disparity of levels of systolic pressure and EP_6 was to be expected. The correlation with diastolic pressure furnishes additional evidence for the validity of the EP_6 method as a measure of vasomotor tone in some regions (higher values of pressure being associated with increased regional tone). This relationship was surprisingly good in the mesentery, better in the hindlimb than the forelimb, and absent in the kidney, indicating a descending order of importance of these structures in the primary regulation of diastolic pressure both in the anesthetized normal and hypertensive state. Theoretically, changes of vasomotor tone in an

* Ordinary variations of venous pressure are of insufficient magnitude to affect levels of EP_6 except when very low values are obtained.[14] In hypertension venous pressure is normal.[13]

† It is known that arterial pressure-volume factors, specifically intra-arterial volume and elastic recoil, are altered in hypertension. Intra-aortic volume may increase 100 per cent.[26] Although changed intentionally during pressure-flow determinations, they influenced primarily the initial or α sections of the gradients of the kidney and forelimb; presumably the gradient of other vascular areas was similarly affected).[16]

‡ While variations in the ratio occur in a given region because of different sizes of dogs presumably they may be disregarded when one compares one series of average regional values with another. No known function or measurement of the gradient provides an accurate index of resistance per se.[15]

§ It is unfortunate that no mesenteric pressure-flow curves were obtained; they are difficult to make valid.

area of high conductance (low resistance and a high rate of blood flow) have greater effects upon total peripheral resistance (TPR) than do variations in beds with the opposite characteristics.[2] However, the effects must be examined on a functional basis. Although both the kidney and mesentery fit into the former category, only the latter can be considered to be of primary importance in the regulation of blood pressure. At rest the fore and hindlimbs are areas of relatively low conductance[2] and, although they assist in the regulatory function, they are probably relatively unimportant in the anesthetized state. Similar conclusions were drawn when maximal vasoconstriction was simulated in the limbs of man.[27]

3. *Patterns of Regional Vasomotor Tone in Hypertension*

Chronic neurogenic hypertension has been ascribed primarily to an increase of cardiac output[18] although slight changes of peripheral resistance have been noted in a few instances.[17, 28] In the present experiments tachycardia was one criterion by which the effectiveness of vagal section was evaluated. According to recent work,[28] tachycardia should be associated with a normal degree of resistance. In our experiments, however, marked increases of EP_6 were found in the mesenteric area; in the others they were less. These findings do not agree with the theory that chronic neurogenic hypertension is solely dependent upon an increase of cardiac output. The onset of acute neurogenic hypertension caused marked rises of EP_6 in all areas studied except the kidney, and the changes were approximately proportional to the increase of pressure. Obviously, readjustments must occur in the limbs when the condition becomes chronic.

As comparable levels of pressure occur in neurogenic and renal hypertension, it would be expected that vasoconstriction would be more severe in the latter condition, cardiac output being normal.[13] Indeed, such was the case, mesenteric levels of EP_6 being similar to the neurogenic conditions, but greater levels were found in the limbs. Although the kidney does not play a primary role in the regulation of pressure (see above), apparently this area may contribute to the increase of total peripheral resistance in renal hypertension. As the total resistance of a local circulation is equal to the sum of its component resistances[29, 30] it is obvious that the Goldblatt clamp is implicated; in addition, intrarenal resistance may be increased. It is obvious that collateral circulation accounted for some of the high values of EP_6, but in general the levels were inversely related to the duration of the hypertension (a few days to 12 months). High levels of EP_6 were found in the single dog with silk perinephritis and at autopsy this kidney was enclosed in a thick fibrous avascular capsule.

If intrarenal resistance is increased in chronic renal hypertension, it is explained most logically by the theory that partial arterial constriction leads to renal ischemia, and, in turn, humoral vasoconstrictor substances are released which constrict the kidney.* Another explanation involves recurrent repeated stimulation of the renal sympathetic vasoconstrictor nerves by the mechanical action of the clamp. It is difficult to believe that this process could be continuous as the nerves probably would be damaged. A third explanation concerns the stimuation of these nerves, centrally or at their endings, by humoral constrictor substances, and resembles the first. Whatever the mechanism, it is possible that a certain element of reversible renal vasoconstriction may accompany renal ischemic hypertension. The previously observed drop of blood pressure across a Goldblatt clamp,[32] which occurs even in the presence of collateral circulation, is confirmed.

The findings in anesthetized animals must be interpreted with caution, as they cannot be applied directly to the unanesthetized state. However, the general patterns found were surprising. In chronic renal hypertension the values of vasomotor tone in the limbs lie between the extremes found in acute and chronic neurogenic hypertension. Consequently if renal hypertension is caused by humoral vasoconstrictor substances, as is believed, their

* Acute experiments have shown that intrarenal constriction does not necessarily follow partial constriction of the renal artery.[31]

effects upon different vascular beds are probably not uniform.

4. *Relative Degrees of Constriction in Different Vascular Beds*

Rough as the calculations of the degree of constriction may be, the results obtained in the femoral, brachial, and renal vascular beds are illuminating (fig. 5). They show that the brachial and femoral areas are constricted relatively more than the renal in normotension and acute neurogenic hypertension. In the latter condition, however, the change of the degree

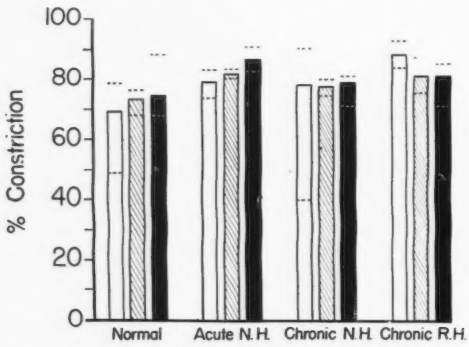

FIG. 5. Degree of regional vasoconstriction in normotension and hypertension. The four groups of columns show the per cent of regional constriction in normotension (normal), in acute and chronic neurogenic hypertension (N.H.), and in chronic renal hypertension (R.H.). The height of the bars indicates per cent constriction in the kidney (open), in the brachial circulation (cross hatched), and in the femoral area (solid). The dashed lines above and below the top of the columns indicate the ranges of variations. All values shown were based on the calculation for r.[16]

of renal constriction is the same as in the limbs. In the chronic state, the renal changes were of wide variation.

According to these calculations normal kidneys are constricted to approximately 70 per cent of capacity, those in acute neurogenic hypertension to 79 per cent, in chronic neurogenic hypertension to 77 per cent, and in renal hypertension, not including the resistance of the clamp, to 89 per cent. Finally the observation that the femoral area is always slightly more constricted than the brachial may be a manifestation of a large muscle mass.[16]

SUMMARY AND CONCLUSIONS

1. Determinations of asystolic arterial pressure gradients were made in four major local circulations of anesthetized normal and hypertensive dogs. In all animals the relationship of vasomotor tone to levels of diastolic pressure was good in the mesenteric area, fair in the limbs, and poor in the kidney, indicating a descending order of importance of these beds in the primary regulation of diastolic pressure.

2. Acute neurogenic hypertension was accompanied by vasoconstriction in all these areas with, however, the renal changing least. On the other hand chronic neurogenic hypertension was primarily characterized by an increase of resistance in the mesenteric area, the other beds being but slightly constricted. Presumably readjustments occur when the condition becomes chronic. Chronic renal hypertension was associated with marked mesenteric vasoconstriction, with the limbs also participating. It is possible that constriction was present in the renal vascular beds.

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Physiologic and Physical Factors that Govern the Clinical Appreciation of Cardiac Thrills

By TIMOTHY B. COUNIHAN, M.D., MAURICE B. RAPPAPORT, E.E., AND HOWARD B. SPRAGUE, M.D.

Palpable cardiac thrills have been considered valuable diagnostic findings. The present study indicates that they add little information to that obtained by careful evaluation of auscultatory findings, and that the quality of cardiac murmurs is a much safer guide in diagnosis than are the palpable vibrations produced by the same mechanism.

CORVISART[1] was among the first to mention and interpret palpable thrills over the precordium as a sign of heart disease. Among the signs of constriction of the orifices of the heart, he mentions "a peculiar rushing like water, difficult to describe, appreciable by the hand applied over the precordium." His pupil Laennec[2] observed that, although such vibrations may be detected by the palpating hand as a thrill, they were much more easily detected by the ear and that in a majority of cases of valvular stenosis it was possible to *hear* an abnormal noise that could not be felt at all with the hand.* This early recognition of the superiority of hearing over touch in the detection of vibrations might be expected to have led to the complete replacement of palpation by auscultation for the perception of vibratory phenomena. However, palpation remains a routine procedure and the palpable thrill has become a physical sign of such diagnostic importance as sometimes to sway the diagnosis.

We are here reporting a study undertaken in an attempt to rationalize the significance of the palpable precordial thrill as a physical sign in clinical medicine.

Sensitory stimulation is aroused as a result of the mechanical contact of the receptor organ with the medium undergoing vibration. The efficiency of detection is directly dependent upon the type of contact or matching impedance as well as the intensity, frequency and the duration of the source vibration with relation to the receptor threshold. Thus, when a cardiac thrill is to be detected with the fingers in the customary clinical manner, all of these factors must obviously play an important role.

The first part of our study therefore was concerned with the quantitative experimental determination of the sensitivity of the fingers to mechanical vibrations of different frequencies under circumstances designed to simulate those of clinical palpation. In the second part of our study, we measured in quantitative physical terms the main frequency and intensity of heart murmurs in a number of patients who had a variety of forms of heart disease. Some of these murmurs were constantly palpable as thrills, some became palpable after special maneuvers were employed and some remained impalpable during the course of the examination. For the three groups, frequency-intensity values were obtained that bore an expected relationship to the threshold of sensitivity of the fingers.

From the accumulated knowledge of the mechanism of production of vibrations in the

From the Cardiac Laboratory of the Massachusetts General Hospital. Presented at the meeting of the First International Congress of Cardiology, Paris, September, 1950.

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* "According to M. Corvisart the principal sign (of 'ossification of the mitral valve') is 'a peculiar rustling sensation, perceived on the application of the hand to the region of the heart.' I have often noticed this symptom. . . . The nearest idea I can give of it is by comparing it to the purring of a cat when pleased. . . . I have frequently found wanting the peculiar vibration in the region of the heart in cases of undoubted disease of the valves. I believe the latter sensation is only perceptible by the hand when the contraction of the orifice is very considerable. . . . (The *murmur* of stenosis of the mitral valve) is well marked when the purring is not perceptible to the hand, but it is much more distinct when this is perceptible and is indeed proportional to its intensity."[2]

circulatory system on the one hand, and of human sensitivity to vibrations on the other, we are enabled, in the light of the data derived from our experiments, to subject the physical sign of cardiac thrill to critical scrutiny and to evaluate its clinical import more exactly than hitherto.

Part I. The Sensitivity of the Fingers to Mechanical Vibrations

The Nature of Vibration Sensibility

A voluminous literature exists dealing with the sensibility to vibrations. While we do not wish to give a full account of it or to enter the lists of its many controversies, it is necessary to review in brief some pertinent points.* Eggers[3] seems to have been responsible for the widespread acceptance of the view that vibrations were a strictly osseous sensation, a view that has since been amply refuted though it is still encountered in recent literature. Von Frey's[4] meticulous studies showed that the vibratory end organ was closely associated and probably identical with the tactile end organ in the skin. Despite Von Frey's apparently convincing studies, Katz[5] propounded the view that the sensibility to vibrations was a separate modality, "the vibration sense," and the controversy that soon arose about this question is as yet not settled. Geldard,[6] using greatly superior apparatus and scrupulous technic, stimulated two populations of cutaneous spots, the one pressure-sensitive and the other pressure-insensitive, with sinusoidal mechanical vibrations and showed an intimacy of relationship between the pressure-sensitive and the vibration-sensitive spots. He concluded that there was no ground whatever for the postulation of a separate vibratory sense. Subsequent experiments by Echlin and Fessard[7] demonstrated that stretch-receptors in tendons responded to vibratory stimulation; they recorded from the exposed nerves supplying muscles and tendons afferent discharges synchronized to the rate of the stimulating fork. They point out, however, that it remains to be demonstrated that such nerve-impulses arouse sensations of vibration in consciousness.

It would appear that vibrations can be received by end organs in the skin and deep tissues and that those in the skin are very closely associated if not identical with the tactile receptors while those in the deep tissues probably include stretch-receptors.

Determination of the Sensitivity of the Fingers to Mechanical Vibrations

Apparatus. Our apparatus for evaluating the tactile threshold consisted of a loud speaker arrangement which was driven by means of an adjustable frequency sinusoidal oscillator. The magnitude of vibration of that portion of the loud speaker upon which the fingers were applied (the rim suspension) was measured both optically and by means of a strain gage during the application of the fingers. Interposed between the oscillator and the loud speaker was an attenuator which the subject under test was allowed to adjust for threshold sensation.

The oscillator possessed a total distortion content of less than 0.1 per cent and the distortion present at the loud speaker rim suspension was so small as not to be observable in a cathode ray oscilloscope which was connected to the strain gage element located (directly under the fingers) at the rim suspension. The relative movements of the loud speaker were detected by the subject under test as a result of placing the fingers in such position that they simultaneously contacted the stationary and moving portions of the rim suspension. The rim suspension simulated the ribs and the intercostal spaces of a human being reasonably well.

Material and Method. Four physicians trained in cardiology were investigated to determine the sensitivity of their fingers to vibrations of sine wave form. Conditions resembled those of clinical palpation in that each observer was permitted to find the optimal pressure for him at each frequency of stimulus and to use a generous area of contact between the distal ends of the four fingers and the vibrating medium. The actual amplitude of the vibrations was directly measured at this pressure of

* An excellent account of the history of the controversy and an exhaustive bibliography are given by Geldard.[16]

the observer's fingers, so that the variable degrees of damping produced by variations in pressure of contact did not interfere with our results. The area of contact was kept about the same for all observers. Thresholds were approached from below only so that fatigue-adaptation effects would not interfere.

Several threshold determinations were made for each subject at the following frequencies: 7, 10, 15, 20, 40, 70, 100, 150, 175, 200, and 300 cycles per second. The mean tactile threshold curve thus obtained and the average human audiogram (after Fletcher) are shown in figure 1 to illustrate the relationship of the finger tactile sensibility to that of the ear. The great superiority of sensitivity of the ear is obvious throughout this range of frequencies, excepting frequencies below the auditory range (i.e. below about 16 cycles per second) where the ear is deaf and the fingers are responsive. At a frequency of 250 double vibrations for example, a vibration which is just audible must be increased 2500 times or 68 decibels to make it just palpable; at 40 double vibrations an increase of 180 times or 45 decibels is necessary.

It is also apparent from figure 1 that the threshold curves for hearing and feeling have different forms. In fact human hearing imposes approximately a logarithmic frequency response in this range while the finger tactile frequency response approximates a cube function. This latter finding has a marked bearing on the relationship of the loudness of a heart murmur as heard to its intensity as a thrill when palpated, which will be considered in more detail.

Discussion. The results of our determination of the sensibility of the fingers agree in general with those reported in the literature that were obtained with reliable technics and apparatus. Thus Gilmer,[8] using the apparatus devised by Geldard and Gilmer,[9] found the frequency-intensity threshold for the fingertip to be a concave one from 64 to 2600 double vibrations with maximum sensitivity for four observers at 256 cycles per second and for the fifth at 512 cycles per second. Large individual differences occurred. Sitzepfand,[10] using a relatively large contactor against the fingertip, found sensitivity to decrease somewhat at 50 to 75 cycles per second, but to increase from there rapidly at first and later slowly to 700 cycles per second, between the limits of frequency of 15 to 700 cycles per second. Knudsen[11] found maximum sensitivity of the fingertip at about 256 cycles per second in the range 32 to 1600 cycles per second. Périlhou and Piéron[12] found sensitivity to increase rapidly from the single tactile impulse to about 100 cycles per second and slowly from 100 to 250 cycles per second to decrease slowly from 250 to 400 cycles per second and rapidly thereafter. The initial increase of sensitivity they found to be effectively a function of the cube of frequency when sinusoidal vibrations are employed. Périlhou[13] later reported similar results but found sensitivity of the fingertip to decrease rapidly at about 550 cycles per second.

While our results are in general accord with those just quoted, exact comparison is not to be expected, inasmuch as we were chiefly concerned with conditions that resembled those of clinical palpation. All the above-mentioned investigators measured sensitivity at the fingertip, which is the region of the body surface most sensitive to vibrations,[8, 14] whereas we employed a larger area of the fingers. Gilmer[8] found in this connection that for vibrations of lower frequency the sensitivity of the fingertip was greater with a larger contactor, but for higher frequencies the area of contact was a negligible factor. Again the findings of Cohen and Lindley[15] that thresholds were lowered by increased pressure on the contactor makes it seem likely that this has introduced another point of difference that makes it hazardous to compare our results with those of others who used fixed pressure of the finger on the contactor.

We confined our investigation of frequency-intensity thresholds to an upper limit of 300 double vibrations because this seemed adequate for the range of frequencies of heart murmurs exhibiting a tactile sense. In our series of phonocardiographic analyses of murmurs to be presented, no "fundamental" frequency above this value was encountered. The upper limit of vibration sensibility is unknown

Knudsen[11] found about 1600 double vibrations to be the upper limit but thought that with greater amplitudes than he had available 3000 or 4000 cycles per second stimuli would be perceptible. Gilmer[8] found a sharp cut-off at 2500 cycles per second. Goodfellow[16] found frequencies of 8192 cycles per second palpable, but his apparatus was imperfect and this figure seems sufficiently out of line to make it questionable. Gault[17] found vibrations above 2000 double vibrations palpable by 2 deaf subjects.

The lower limit of frequency of sensible vibrations is logically the single stimulus, but some investigators have reported that the distinctive sensation of vibration is not aroused until higher frequency is achieved. Knudsen[11] thought this point lay between 12 and 18 cycles per second, and Lalanne[18] and von Stramlick[19] found 10 cycles per second as the lowest fusion point. The frequency response of our apparatus was not reliable below 7 double vibrations but at this frequency all observers agreed that a sense of vibration was aroused.

The superior sensitivity of the ear at the frequencies investigated has been discussed, excepting frequencies below about 16 to 20 double vibrations. The ear is also superior in its ability to distinguish small changes in *frequency*: a change of 1 per cent or less is appreciable by hearing while 15 to 30 per cent change is necessary for appreciation by the fingertip (Knudsen). Dunlap[20] found a 5 per cent difference of frequency appreciable to the tactile sense at frequencies of 420 to 460 double vibrations but often misinterpreted as a change of intensity.

The ability to detect changes of *amplitude* with the fingertip closely approaches that with the ear. Knudsen[11] says that the cochlea and tactile nerves can both just barely distinguish a fractional change of amplitude of approximately one tenth at low intensities and one twentieth at high intensities.

Cold decreases the sensitivity to vibrations[21] as do age[14, 21, 22] and certain well known neurologic disorders.[23] Thresholds are subject to occasional variations in the same individual and may exhibit wide divergence in different individuals.

The effects of fatigue have been studied by Wedell and Cummings[24] who found that sensitivity to vibratory stimuli applied to the palm of the hand was reduced by 5 to 15 decibels after three minutes' continuous stimulation. Kampik[25] was able to produce complete fatigue of the vibration sensibility after an hour's vibratory stimulation.

Clinical Application. The major portion of the energy of heart sounds and murmurs lies well within the frequency band of 7 to 300 cycles per second and their main vibrations will be palpable if they are of sufficient intensity and duration. The vibratory character of the first and second heart sounds is not ordinarily appreciable by palpation though the intensity may be adequate, because the duration of the main frequency components is too short. Exceptionally, however, it may be so appreciated when the heart sounds last abnormally long, as will be seen later in the phonocardiographic analysis of thrills.

The subjective estimate by hearing of the degree of loudness of a murmur will not exactly parallel the estimate of its intensity to palpation, as is evident from the divergence of the curves of threshold of hearing and feeling (fig. 1). The clinical observer can usually predict by auscultation whether a particular murmur will be appreciable as a thrill, but occasionally two murmurs may seem to the ear to be of equal intensity while only one is palpable as a thrill. Indeed, in such case the impalpable murmur may seem the slightly louder to auscultation. For this reason it is psychologically unsound to employ the palpability of murmurs in their auscultatory grading by loudness. The finding of or failure to find a thrill accompanying a loud murmur thus becomes a matter of academic curiosity.

It is necessary to qualify this conclusion by calling attention to the fact that we have employed *pure* sine waves in our experiments, while murmurs and thrills are 'noises', that is, composed of a medley of tones of various frequencies and intensities. Whether the threshold of sensitivity of the fingers for noises is very different from their threshold for pure tones is not answered by this study.

Part II. The Phonocardiographic Analysis of Murmurs and Thrills

Forty patients who had heart murmurs of loud intensity were selected for study, irrespective of the type of heart disease from which they suffered. All were first examined clinically and note was made of the grade of intensity of the murmurs and of the presence and grade of thrills. The grading of murmurs was made according to the recommendations of Levine[26] from six possible grades, without regard to the presence or absence of thrills. The thrills were graded under four heads, from the faintly palpable grade 1, which often required special maneuvering of the patient for its detection, to the very marked grade 4, which is a strong purr often palpable through a light garment. The grade 2 thrill was constant and easily felt without arousing a marked sensation, and the grade 3 was of marked intensity and felt immediately with the palpating hand. In the 40 patients no grade 6 murmur was encountered and no grade 4 thrill. That the palpating finger is a good analyzer of different grades of intensity has already been mentioned and it is possible to recognize with comparative ease four grades of intensity of clinical cardiac thrills.

Phonocardiograms were then taken on each patient and subsequently analyzed to discover the main frequency and intensity of the murmur vibrations. The apparatus employed was the Sanborn Tribeam. Stethoscopic registration was employed in the phonocardiographic channel.[27] The large open bell chestpiece having a diameter of 5 cm. and an internal volume of 12.7 cc., was used throughout. After each recording and without altering the amplification of the machine, a standard signal of 500 double vibrations at 90 decibels at source was sent through the channel and recorded so

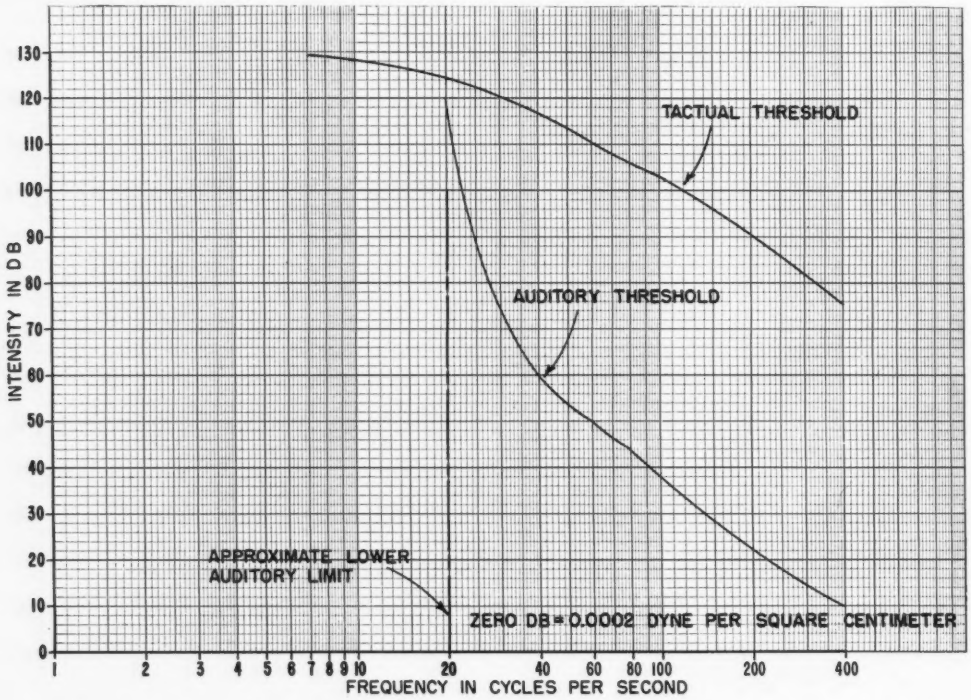

Fig. 1. The mean tactile threshold curve of the fingers of 4 physicians trained in cardiology and the mean auditory threshold curve.

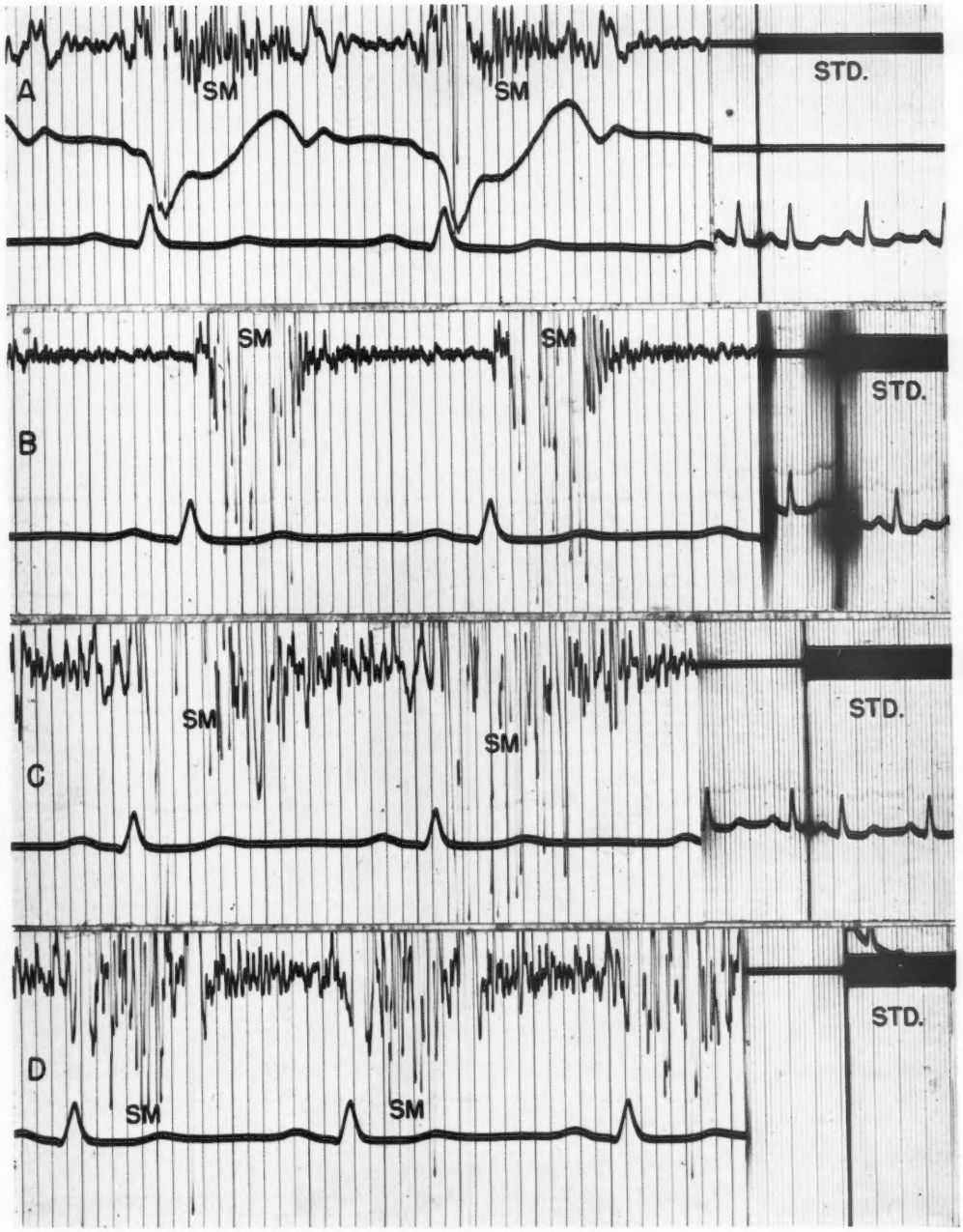

FIG. 2. Phonocardiograms of case 36. Stethoscopic records with large open bell chest piece, taken at the following areas: (*A*) apex, (*B*) aortic area, (*C*) pulmonary area and (*D*) left sternal border in the fifth intercostal space. After each recording from the patient the base line of the sound recording channel is registered and then the standard signal of 500 cycles at the same amplification as the patient-record.

TABLE 1.—*A Comparison of the Clinical Findings with the Quantitative Measurements Obtained by the Phonocardiographic Method.*

NO.	CLINICAL FINDINGS						PCG ANALYSIS		REMARKS
	DIAGNOSIS	POST. & RESP.	MURMUR			THRILL	FREQ.	INTENSITY	
			Site	Timing	Grade	Grade	d.v.	db.	
1	Ventricular Septal Defect	——	3rd Lics	Systolic	4	+	110	122.6	
2	Ventricular Septal Defect	——	Apex PA 3lics	Systolic " "	4 4+ 4+	1+ 2 2	110 110 110	117.7 118.5 126.0	Murmur & thrill maximal at 3rd left intercostal space.
3	Luetic Aortitis	——	Apex Apex	Systolic Early Diast.	3 3	0 0	110 75	93.5 96.0	
4	Congenital Heart Disease	——	Apex	Diastol.	4	+	150	112.5	
5	Cor Pulmonale	——	Apex	Systolic	3	0	150	84	
6	Patent Ductus Arteriosus	——	PA PA	Systolic Diastol.	4 4	+ +	110 100	126 112.6	Continuous murmur
7	Aortic Stenosis	——	Apex PA	Systolic "	2 3	0 0	135 125	85.7 97.6	
8	Mitral & Aortic Stenosis	——	Base	"	4	+	150	114.0	
9	Mitral Regurgitation	——	LSB	"	3	0	170	75.5	
10	Ventricular Septal Defect	——	Apex LSB3	" "	4 5	1 2	110 185	106.8 104.0	Lower actual intensity at LSB despite subjective impression
11	Pulmonary Stenosis	——	PA	"	5	2	150	110	
12	?Mitral Regurgitation	——	Apex	"	3	0	100	104.5	Short murmur, $\bar{c}$ main vibrations of 0.06 sec. duration.
13	Ventricular Septal Defect	——	Apex	"	3	0	125	88.14	
14	Mitral Stenosis & Regurg.	——	Apex Apex	" Diastol.	3 4	? + 3	100 55	112.7 120.1	Thrill felt by some observers
15	Aortic Regurg.; Mitral Stenosis & Regurg.	——	LSB4 Apex	Early Diast. Systolic	4 3	0 0	150 50	86.5 114.6	
16	Mitral Stenosis & Regurg.	——	Apex	Systolic	4	2	225	105.1	
17	Ventricular Septal Defect	——	Apex	"	5	3	125	113.0	
18	Lutembacher's Disease	——	Apex	Presystolic	4	2	75	114.0	P-R interval 0.21 sec.
19	Mitral Stenosis	——	Apex	Mid-Diast.	4	+	125	99.5	
20	Aortic Stenosis	——	Apex	Systolic	4	+	125	109.0	
21	?Ventricular Septal Defect	——	Apex	Systolic	3	0	175	97.9	
22	Luetic Aortis: A.R.	——	"	"	3	0	175	76.0	
23	Mitral Regurgitation	——	"	"	4	?	100	102	Evanescent faint thrill
24	Mitral Stenosis & Regurg.	— Apex6ics Apex " Apex5ics	" Middiast "	3 3 4	1 0 2	100 50 50	108.0 101.6 109.0	The sharp localization of the mid-diastolic murmur & thrill to the 5th intercostal space is noteworthy.
25	Mitral Stenosis	——	Apex	"	3	2	100	109.6	
26	Congenital Heart Disease	——	"	Systolic	4	+	100	103.6	
27	Luetic Aortitis $\bar{c}$ A.R.	——	" "	" Early dias.	3 2	0 0	75 50	76.6 73.1	
28	A-V Aneurysm Pulmonary	——	"	Systolic	3	0	125	77.8	
29	Congenital Aortic Stenosis	——	Aortic PA Apex	" " "	5+ 5 5-	3 3- 2+	125 125 125	120.4 116.5 113.5	Murmur & thrill max. at Aortic area, diminishing intensity from there.
30	Patent Ductus Arteriosus	——	Apex	"	4	1	125	110	
31	Aortic Stenosis	——	Aortic	"	4	+	200	114.3	
32	Tetralogy of Fallot	——	PA	"	4	+	190	101.1	
33	Luetic Aortic & Regurg.	——	Apex	"	3	0	138	86	
34	Mitral Sten. & Regurg.	——	Apex	presyst	4	1	100	117.8	Duration of Presystolic murmur 0.08 sec. + first sound 0.12 sec. = 0.20 sec.
	Aortic Sten. & Regurg.	15° norm. expir. 110° " "	Aortic "	diastolic "	3 3+	0 0	138 138	96.0 99.5	Leaning forward increases intensity.
		15° deep expir. 15° norm. " 110° " "	" " "	Systolic " "	4- 4 4+	0 1 2	100 100 100	106.1 109.1 116.8	Expir. & leaning forward increases intensity.
35	Aortic Stenosis	25° " " 80° " " 120° " "	" " "	" " "	4 4 4	0 0 1	110 110 110	107.3 107.3 109.1	A faint thrill is felt when leaning forward.
36	Aortic Sten. & Regurg. ?Pulmonary Stenosis	——	Apex Aortic PA LSB5 "	" " " " Diastol.	4 5 5 4 3	0 3 3 0 0	88 88 88 88 100	108 120.4 120.7 112.6 94.35	Systolic murmur & thrill were of very nearly equal intensity at Aortic & Pulm. areas.
37	Aortic Regurg.	——	LSB	"	3	0	75	106.9	
38	Complete Heart Block	——	Apex	Systolic	3	0	125	85.4	
39	Mitral Stenosis	——	"	Diastol.	4	0	75	99.5	
40	Pulmonary Stenosis	——	PA	Systolic	4	1	87	108.4	

as to provide a standard against which to measure the intensity of the murmur.[28] An illustrative record is shown in figure 2. The frequencies and amplitudes of the main vibrations of the murmurs and the amplitudes of the standard signals were measured from the records. The ratio between amplitude of the main deflections of the murmur and the amplitude of the deflections of the standard signal was calculated in each record and correction made for

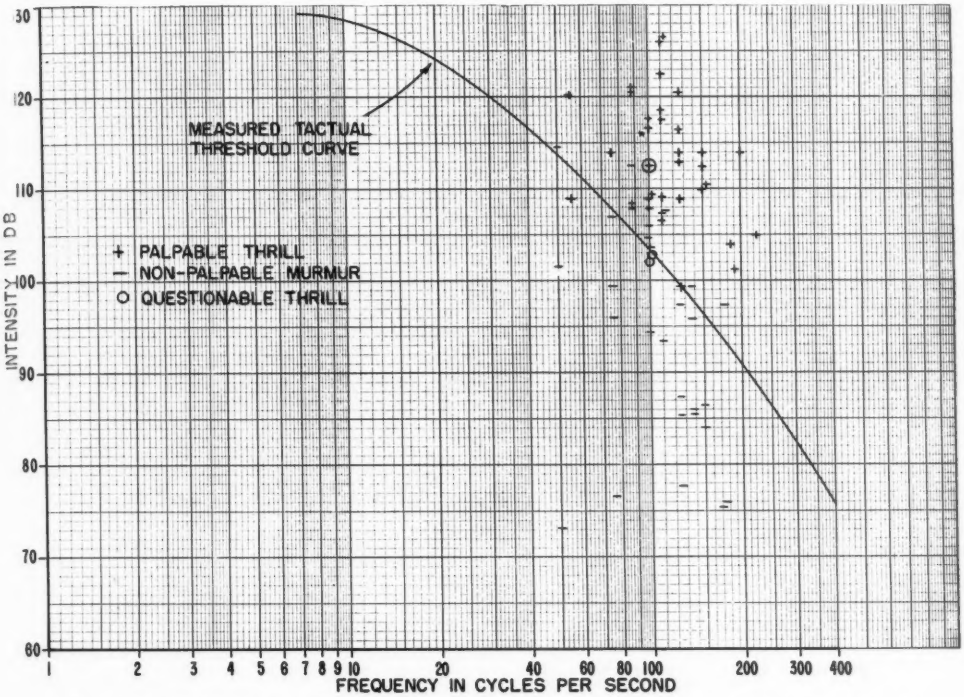

FIG. 3. A graphic representation of palpable and impalpable thrills as judged clinically with relation to the tactile threshold curve of the fingers of 4 physicians trained in cardiology.

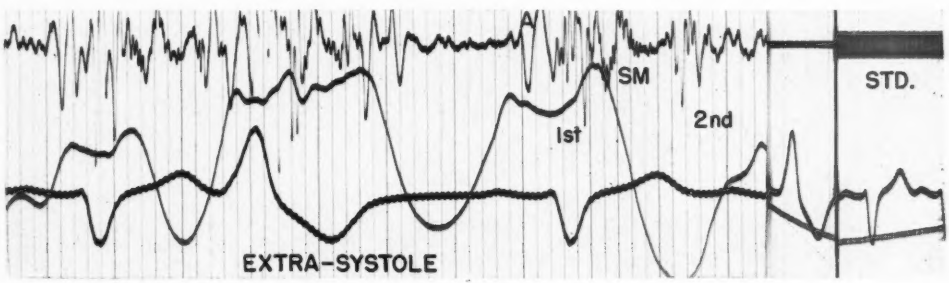

FIG. 4. Stethoscopic phonocardiogram at apex of subject with syphilitic aortitis and aortic regurgitation. The first sound increases in duration and intensity when a ventricular extrasystole occurs. An atrial sound and a systolic murmur are present. Normally no thrill was noted, but with each extrasystole the component vibrations of the first sound became clinically palpable as a brief thrill-like phenomenon superimposed on the thrust of the apex beat.

the stethoscopic response. This derived voltage ratio is directly convertible into decibels, and gives the quantity in decibels by which the murmur exceeds or falls short of the intensity of the standard signal, which in all cases was set at 90 decibels. The decibel scale here employed refers to a reference of zero decibels which represents a sound pressure of 0.0002 dyne per square centimeter applied to the ears.

The data pertaining to the 40 subjects are presented in table 1. It may be seen that in some subjects the intensity of the murmur was significantly altered by certain maneuvers of the patient and that a thrill could sometimes be elicited in certain postures of the patient and not in others. In such cases phonocardiograms were taken in these various positions and in different phases of respiration, and the results are presented. The table also shows the diagnosis of the causative lesion in each case.

In figure 3, the results of phonocardiographic analysis are related to the curve of threshold sensitivity of the fingers as experimentally determined. It may be observed that the palpable murmurs fall on the one side of the threshold curve, while those that were impalpable fall on the other. The deciding factors in determining their palpability, therefore, were the frequency-intensity values of the vibrations and not the nature of the causative lesions.

It will be recalled that in addition to the frequency-intensity value of vibrations, their duration is a determining factor with regard to palpability. The duration of all murmurs studied except one was sufficient to render them palpable as thrills when the frequency and intensity were adequate. From the analysis of phonocardiograms, it became apparent that the intensity and frequency of the first heart sound were often such as to render it probable that their main component vibrations should be palpable as a brief "thrill"; but on clinical palpation no such "thrill" could be felt except in one case in this series. This case seems worthy of individual description.

During the clinical examination of the patient, who had syphilitic aortitis, premature beats were noted occasionally in an otherwise normal rhythm. There were a grade 3 aortic diastolic murmur and a grade 2 systolic murmur at the base of the heart, and a grade 2 systolic murmur at the apex, with no thrill in any region. The apex beat was not unusual and during the regular sinus beats the component vibrations of the first sound were not palpable; but with each premature beat a short thrill became palpable superimposed on the apex beat. On auscultation, the first heart sound was not unusual except that each premature extrasystole was accompanied by an unusually loud and prolonged first sound. A phonocardiogram was taken and the stethoscopic record at the apex is shown in figure 4. When the mechanism is of sinus origin the first sound has a frequency of 100 cycles per second and an amplitude of 107.7 decibels and lasts about 0.12 second; the extrasystolic first sound is of the same frequency but is of greater intensity (115.7 decibels) and of longer duration (0.20 second).

It is not uncommon to find first heart sounds of sinus rhythm equal to those produced by ventricular extrasystoles, but in such a case the duration of the first sound is generally shorter. Therefore the increased duration appears to be the factor which made the vibrations palpable. It is possible that the single impulse of the apex beat may exercise a masking effect upon the higher frequency sound vibrations, but the present case suggests that the chief factor is the brevity of duration of the *main* frequencies of the normal first sound.

Certain other cases require mention individually.

It will be noted from table 1 that the murmur in *case 12* falls into the expected range of palpability, having a main frequency of 100 cycles per second and intensity of 104.5 decibels, but no thrill was felt. The main frequencies here were of this intensity for only 0.06 second and of much less amplitude during the rest of systole. Here again it seems probable that their duration at ample intensity was insufficient for the clinical palpation of a thrill.

Case 34 (fig. 5) illustrates the effects of variations of posture and respiration on the intensity of murmurs and thrills and the clinical necessity of employing these maneuvers in such cases in order to elicit a thrill. It will be noted also in this case that the duration of the presystolic murmur (0.08 second) was probably alone too short for its appreciation as a thrill, and that the perception of the thrill depended on feeling the presystolic vibrations plus the main vibrations of the first sound (duration 0.12 second). It is probable that this is true of the presystolic murmur in general: that neither its own duration nor the duration of the first sound alone are sufficient to render either palpable, but that the sum of both is responsible for the effect of a thrill

However, when the A-V interval is abnormally long, as in *case 18*, (P-R interval 0.21 second), the presystolic murmur itself may be of sufficient length to arouse the sensation of a thrill.

5; a thrill of grade 2 intensity was felt in this location. At the apex the murmur was considered to be less intense and was graded 4, with a thrill of grade 1. The phonocardiogram showed that a considerable

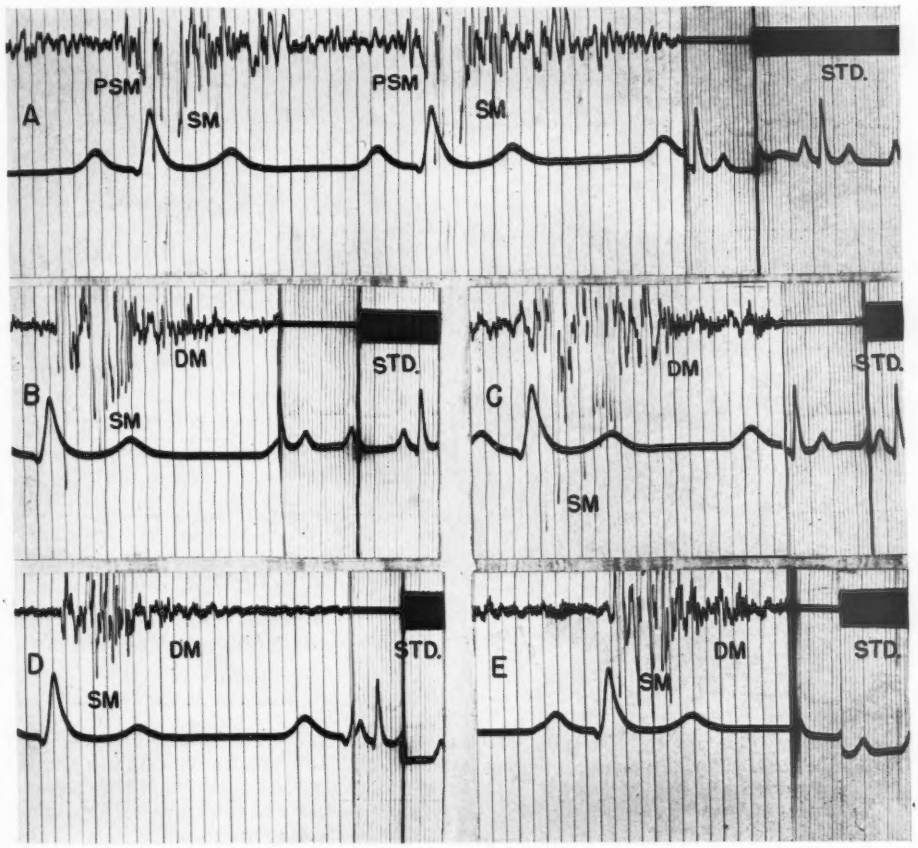

FIG. 5. Phonocardiogram of case 34 (mitral and aortic stenosis, mitral and aortic regurgitation), showing the effects of alterations of posture and respiration on the intensity of the murmurs. (*A*) Apex record. Subsequent records were taken at the aortic area as follows: (*B*) at end of normal expiration with subject 15 degrees from horizontal; (*C*) same phase of respiration, 110 degrees from horizontal (that is, leaning forward); (*D*) at deep inspiration in the same posture; (*E*) after a deep expiration in the same posture.

The phonocardiograms of *case 35* are demonstrated in figure 6. A thrill was felt only when the patient leaned well forward, as is common in aortic stenosis.

Case 10. This patient had congenital heart disease probably with an interventricular septal defect. A systolic murmur was audible all over the precordium and was considered loudest at the left sternal border in the third intercostal space where it was graded

difference of frequency existed between the murmurs at both locations, that at the left sternal border having a main frequency of 185 cycles per second and the apical murmur a frequency of 110 cycles per second. The actual intensity of the apical murmur was 106.8 decibels and that of the murmur at the left sternal border 104 decibels despite the clinical impression of greater loudness of the latter and of greater intensity of the thrill at the left sternal

border. This subjective error is attributable to the higher frequency of the vibrations at the left sternal border and is readily understandable by reference to the threshold curves of hearing and feeling. This condition will not arise when a single murmur maintains its frequency at different locations of conduction. In *case 10*, it seems likely that one was dealing with two distinct murmurs. In *case 2*, the murmur of a ventricular septal defect is traced from its site of maximal intensity at the left sternal border to two areas of conduction, namely apex and pulmonary area. It may be seen from table 1 that the frequency is the same in all three areas and that the subjective impression of loudness of the murmur and intensity of the thrill correspond to the actual intensity of the vibrations at each area.

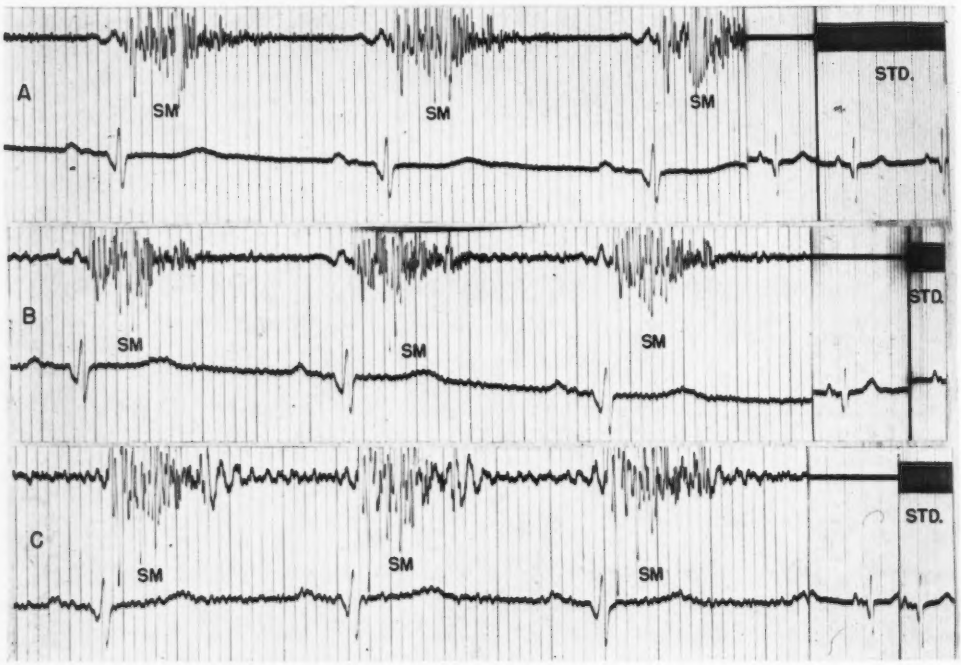

FIG. 6. Phonocardiogram of case 35 (aortic stenosis) showing the effect of posture on the intensity of the vibrations of the aortic systolic murmur as recorded at the aortic area. Breath was held at the end of normal expiration throughout, with the following alterations of posture: (*A*) 25 degrees above horizontal (intensity of murmur 107.3 decibels), (*B*) 80 degrees above horizontal (intensity 107.3 decibels) and (*C*) 120 degrees from horizontal, that is, leaning forward (intensity 109.1 decibels). A slight thrill became palpable in the last position.

It is necessary to point out certain shortcomings in our experiment. The modifications of frequency response introduced by the large open bell chest-piece[27] are not accounted for, and a possible advantage that the physician may gain in the search for the cardiac thrill by pressing his fingers into the intercostal spaces was lost to our instrument because the diameter of the chest-piece did not allow of its being so inserted between the ribs. Attention has already been called to the possibility that the sensitivity of the fingers to vibrations may not be quite the same for complex noises as for pure tones. Stethoscopic registration permitted only the main vibrations of the murmurs to be quantitatively studied and it is conceivable that a harmonic analysis would modify somewhat the end result.

Discussion

While the intimate nature of the mechanism of production of murmurs and thrills in the

heart and blood vessels remains the subject of some speculation, a large body of evidence exists to show that the vibrations are produced by eddies in the stream of blood. Eddy formation occurs by election at the site of an obstruction and the configuration of the obstruction, as well as the velocity of flow, viscosity of the fluid and caliber of the vessel or chamber, exerts an important influence on eddy formation. Eddies may, however, form to a marked extent in the absence of distinct obstruction in tubes of even bore; in such instance fluid flow is streamlined below a certain velocity but may become turbulent and form eddies when the critical velocity is exceeded. Such eddies may give rise to vibrations that are audible and palpable, as in the collaterals in coarctation of the aorta.

Our study has been concerned with elucidating the factors that determine the palpability of vibrations that originate from the turbulent flow of blood in the circulatory system. Their palpability, like their audibility, depends on certain physical properties of the vibrations: frequency, intensity and duration; but the threshold values for the sense of touch are higher than those for hearing and it follows that when a superior sensory mechanism (hearing) is available for the perception of the same physical phenomenon it should replace the inferior (palpation) in the clinical examination of the patient. We have not encountered murmur vibrations below about 16 cycles per second where the human tactile sensation is keener than the audible. Actually, 50 cycles per second was the lowest murmur frequency encountered which is well above the lower limit of about 16 cycles per second.

The truth of this has been increasingly realized in clinical medicine and no reluctance is now felt, for example in diagnosing aortic stenosis without feeling, the classic thrill, and it has become obvious too that the diagnosis of ventricular septal defect must frequently be made from the murmur and other features in the absence of a thrill, though the latter will often be found if sought for. On the other hand, the finding of a thrill accompanying a murmur does not immediately stigmatize the murmur as belonging to a sinister category. It is possible to discover an 'inorganic' thrill, as in cases of cor pulmonale without valvular disease of the heart, when it must be interpreted as being no more sinister nor more 'innocent' than the murmur, since both are but different percepts of the same physical phenomenon.

Summary and Conclusions

1. A study was undertaken to estimate the significance and value of the cardiac thrill as a physical sign in clinical medicine.

2. The threshold of sensibility of the fingers of 4 physicians to vibrations in the range of frequency of the main cardiac vibrations was experimentally determined, under conditions resembling those of clinical palpation.

3. Forty patients who had loud or moderately loud cardiac murmurs were examined clinically and the murmurs and thrills were graded. Phonocardiograms were then taken and analyzed to discover the frequencies and intensities of the vibrations.

4. The ear appreciates the intensity of murmur vibrations as a degree of loudness that approximates but does not exactly parallel the impression of intensity of thrill as detected by the fingers.

5. The sensitivity of the fingers to vibrations in the range of cardiac murmurs is so far inferior to that of the ear that the elicitation of a cardiac thrill becomes a matter of academic curiosity and yields no information of diagnostic import that is not obtained by auscultation. The perception of a thrill depends on the sensitivity of the fingers of the observer and on the physical properties of the vibrations, namely their frequency, amplitude and duration, and tells no more about the nature of the underlying lesion than can be learned by the ear from these same properties.

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The Action of Several Cardiac Glycosides on Conduction Velocity and Ventricular Excitability in the Dog Heart

By Gordon K. Moe, M.D., and Rafael Méndez, M.D.

The effects of digitoxin, ouabain, lanatoside C and K-strophanthoside on ventricular excitability and conducion velocity were studied. All agents caused an initial slight increase followed by a decrease of ventricular excitability, and depression of A-V and intraventricular conduction. Conduction, while depressed in the specialized tissue, was well maintained in the muscle itself until death of the heart. No significant qualitative differences between the glycosides were observed.

AMONG the cardinal differences between the various cardiac glycosides are the speed of onset of action, the degree of absorption from the intestine, and the rate of elimination. The importance of such differences in the clinical use of digitalis and strophanthus preparations is too well recognized to need further emphasis. Other differences have been proposed without, as yet, gaining widespread confirmation. Moe and Visscher[1] studying the actions of the pure glycosides of digitalis lanata in the heart lung preparation, observed wide differences in the ratio of toxic dose (dose causing ectopic rhythms) to "therapeutic" dose (smallest dose causing a measurable increase of mechanical efficiency in the failing heart) for the three substances. Their conclusions were not confirmed by Cattell and Gold,[2] who carried out somewhat similar assays on the isolated papillary muscle, or by Farah and Maresh,[3] who used the heart-lung preparation but administered the glycosides by continuous infusion. If one assumes that the toxic activity represents an "extension" of the therapeutic action,[2] one would not expect significant differences in the "therapeutic ratio". However, it does not seem necessary to make such an assumption. For example, both quinidine and digitalis are capable of producing ectopic rhythms and fibrillation, yet the former has a negative, and the latter a positive inotropic action on the muscle.

Occasional reports in the clinical literature suggest that various preparations are not identical in their cardiac actions. Chavez,[4] on the basis of wide experience with ouabain and digitoxin (Digitaline Nativelle), believes that the former agent is particularly useful for its positive inotropic action in acute congestive failure with regular rhythm, whereas the digitalis glycoside is more active in reducing the ventricular rate in patients with auricular fibrillation. Similar observations have been made by Codina.[5] Since ouabain is used only rarely in most clinics in the United States, little support for this concept may be found in the North American journals. Chavez' observations would suggest that depression of A-V conduction is a characteristic more prominently displayed by Digitaline than by ouabain.

In an attempt to determine whether important differences exist between the effects of various glycosides on excitability and conduction velocity, a comparative study of digitoxin, lanatoside C, ouabain, and K-strophanthoside was carried out.

Methods

Dogs of both sexes weighing from 6 to 12.5 Kg. were prepared under intravenous chloralose anesthesia. The chest was opened in the midline and the pericardium was opened widely and fixed to the edges of the sternum. Artificial respiration was maintained at a volume which just failed to abolish activity of the respiratory muscles, and was adjusted frequently in order to ensure a reasonably constant

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level of arterial oxygen and carbon dioxide. Electrical stimuli from a Grass stimulator were introduced to the right auricle through a pair of electrodes attached to the margin of the appendage, or to the right ventricle through electrodes attached to the pulmonary cone. Recording electrodes were attached to the right auricle, to two points on the surface of the right ventricle in line with the stimulating electrodes, and to a point near the apex of the left ventricle. (See fig. 4.) Records were taken by means of a Grass six-channel ink-writing electroencephalograph. One channel was used to record the stimulus, one to record the auricular response, one (connected to A and V_3) to record A-V conduction

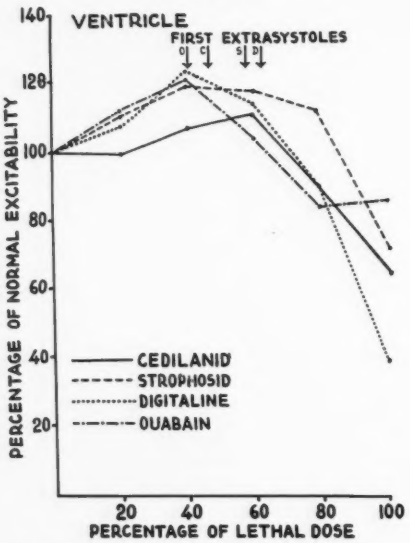

FIG. 1. Excitability of right ventricle plotted as percentage of the control value (inverse of threshold voltage). Values for each glycoside represent average of three experiments.

time, and the others to record responses at the three ventricular electrodes.

Excitability of the ventricle was determined, as described previously,[6] by estimating the threshold voltage necessary to drive the heart at a shock duration of 0.05 millisecond. Conduction time was estimated by measuring the delay between the stimulus artefact and the electrical response at the various points. It was recognized, of course, that conduction *velocity* cannot be accurately measured by this means, since the actual path traveled by the wave front cannot be determined.

In an effort to eliminate differences between the glycosides due to variations in their speed of action, the drugs were administered at 30 minute intervals in doses estimated to be 12 to 16 per cent of the "acute" lethal dose. The experiments therefore lasted from three to six hours. Observations of excitability, conduction time, and spontaneous activity were made after each fractional dose. This technic of administration necessitates the use of relatively large doses of a slowly acting agent such as digitoxin, and the quantitative differences observed therefore are of little significance.

RESULTS

1. *Ventricular Excitability.* The course of changes in ventricular excitability is illustrated in figure 1. The curves are plotted as averages of three experiments for each drug. To enable

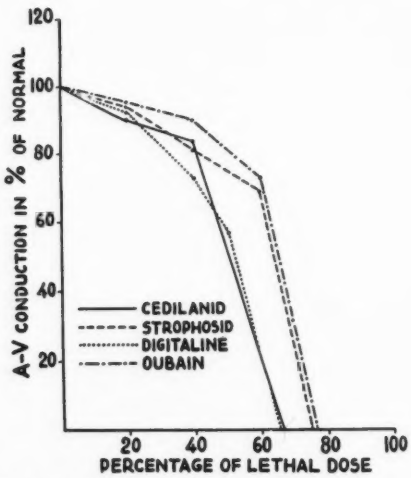

FIG. 2. A-V "conduction" plotted as percentage of control value (inverse of A-V time interval).

plotting on a common scale, the time of cardiac death in each experiment was taken to represent 100 per cent of the lethal dose. Since fractional doses were administered at regular intervals, 20 per cent of the *time* intervening between the first dose and cardiac death was taken to represent 20 per cent of the lethal dose. On the ordinate scale, the initial value of electrical excitability (inverse of the threshold voltage) was assigned a value of 100, and changes are plotted as per cent of the normal initial value. Similar conventions were used in the construction of figures 2 and 3.

In every case an initial slight *increase* of excitability occurred, and excitability was maintained until well over half the lethal dose

had been administered. After 60 to 80 per cent of the lethal dose had been administered, excitability declined progressively to reach values of 40 to 80 per cent of normal shortly before death. In every experiment it was still possible to drive the ventricle up to the time when ventricular fibrillation terminated the experiment.

In all experiments ectopic beats of ventricular origin appeared after the injection of 40 to 60 per cent of the lethal dose, at a time when ventricular excitability was slightly enhanced.

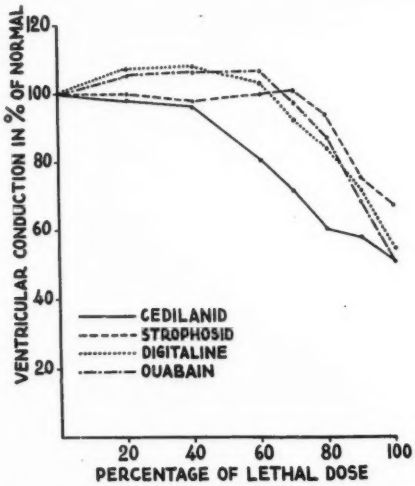

FIG. 3. Intraventricular conduction plotted as percentage of normal "rate" (rate = inverse of time interval between responses at point V_1 and V_3, figure 4).

Idioventricular beats occurred with increasing frequency as the experiments progressed, until shortly before or at the time of auricular arrest, at which point an irregular ventricular rhythm occurred, usually at a frequency exceeding the normal sinus rate. There were no significant qualitative differences between the glycosides.

2. *Atrioventricular Interval.* As expected, all agents prolonged the A-V interval (as measured between the right auricle and the apex of the left ventricle). The response is charted as conduction "rate" (inverse of time) in figure 2. Complete block, indicated by failure of the ventricle to respond to stimuli applied to the right auricle, occurred at from 65 to 75 per cent of the lethal dose. Block always developed before the auricle itself became unresponsive to stimuli. Digitoxin and lanatoside C uniformly caused A-V block earlier than the strophanthus glycosides, but the difference is of questionable significance with the small number of experiments.

3. *Ventricular Conduction.* Ventricular conduction rate was estimated by driving the ventricle with shocks of twice-threshold strength and measuring the time interval between the shock artefact and the appearance of electrical activity at each of the ventricular electrodes.

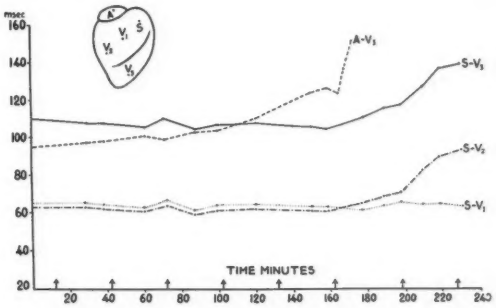

FIG. 4. Effect of K-strophanthoside on conduction. Exp. 7, 7/28/48. Dog 7.5 Kg. Time intervals between shock artefact and response at points V_1, V_2, and V_3 plotted against time; stimuli applied at S. The curve labeled A-V_3 represents time between the auricular and ventricular components of an electrogram taken between points A and V_3; stimuli applied to right auricle. At each arrow, injection of 0.175 mg. K-strophanthoside.

Since this measure includes *latency* at the stimulated point as well as actual conduction time, the values plotted in figure 3 represent the inverse of the time between excitation at point V_1 and V_3. (See figure 4.) This value reflects the average rate over a path which includes both Purkinje and muscular tissue.

With Digitaline and ouabain a slight acceleration of conduction velocity occurred early in the course of the experiments, but the difference between these agents and Cedilanid is probably insignificant. As was true of ventricular excitability, conduction within the ventricle was well maintained, and was slowed much later than A-V conduction.

In most experiments, the point of electrode

V_1 (fig. 4) was within 12 mm. of the stimulating electrode "S." In every case, the stimulus-response interval at this near point failed to increase. A typical experiment is illustrated in figure 4. While the stimulus-response interval for the more distant points V_2 and V_3 began to increase rapidly after 160 minutes (about two-thirds of the lethal dose), conduction to the nearer point was maintained at a normal level until death occurred.

4. *Idioventricular Activity.* All agents caused ventricular extrasystoles increasing in frequency until a multifocal tachycardia developed. With ouabain occasional extrasystoles appeared on the average earlier than with the other agents at about 40 per cent of the lethal dose, while with digitoxin this manifestation of increased automaticity was delayed until a little more than 60 per cent of the lethal dose (fig. 1). A similar difference between ouabain and digitoxin was described by Krueger and Unna in the cat.[7]

Discussion

No major qualitative differences between the four glycosides, representing four different plant sources, were apparent in the limited number of experiments carried out in this study. However, the agents were compared in terms of fractions of the ultimate lethal dose for each, a method of comparison which might be expected to minimize qualitative differences since in each case the functional changes measured represent actions which may be considered to be toxic manifestations contributing eventually to death of the heart. If depression of conduction, depression of excitability, and the initiation of ectopic foci of activity in the ventricles may be assumed to be responsible for the disorganization of ventricular rhythm leading to death, one would expect that these functions would be similarly altered by all the glycosides. These results should not be interpreted to mean that no important differences in the myocardial actions exist. It is probably true that doses of the cardiac glycosides used in the careful treatment of heart failure are well below 35 per cent of the lethal dose, a dose range at which no important alteration of conduction rate or excitability occurred in these experiments. The possibility remains that the positive inotropic action, which is of major importance in the therapeutic use of these agents, may not correlate well with the toxic actions studied here. The clinical differences between ouabain and digitoxin observed and emphasized by Chavez may be due to differences in speed and duration of action, and to differences in the degree of improvement of myocardial contractile strength effected by these two agents. However, Mendez and Pisanty, using technics similar to those of the present study, have observed a significantly greater depression of A-V conduction with digitoxin than with ouabain.[8]

The data presented above serve to emphasize a characteristic of digitalis action which is all too frequently misinterpreted. The statement is commonly made (as in various textbooks*) that extrasystoles, bigeminal rhythm, and ventricular tachycardia occurring as a result of digitalis intoxication represent an expression of increased "excitability" or "irritability" of the myocardium; the implication is made that such idioventricular activity develops *because* the ventricle is more irritable. That this conclusion is invalid can easily be demonstrated. Reference to figure 1 will indicate that the first idioventricular beats occurred at a time when the electrical excitability of the ventricle was indeed slightly increased (threshold voltage slightly diminished), but in our experiments, while ectopic beats *began* to appear at a time

* From Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, 1941, p. 520: "The cause of the ectopic beats is the increased irritability of the myocardium. . . ." From Sollmann, *A Manual of Pharmacology*, ed. 6, 1944, p. 531: ". . . the *muscular excitability* becomes greater and greater; so that the final effects are mainly muscular (increased tone, heightened irritability, spontaneous ventricular rhythm, extrasystoles)." From Krantz and Carr, *Pharmacologic Principles of Medical Practice*, 1949, p. 713: "The cardiac manifestations that may occur are extra ventricular systoles resulting from a hyper-irritability of the heart."

A more accurate statement can be found in Movitt's monograph, *Digitalis and other Cardiotonic Drugs*, 1949, p. 40. Discussing the initiation of ectopic rhythms by digitalis, he says, "All depressors of cardiac excitability, including quinidine, may cause ectopic rhythms when given in large doses."

of enhanced excitability, they became more and more frequent as excitability diminished, leading to a ventricular multifocal tachycardia at a time when ventricular excitability was below normal values, and terminating in ventricular fibrillation at a time when ventricular excitability was, on the average, less than 70 per cent of normal. The error is probably one of terminology. The physiologist quantitates excitability essentially as the inverse of the stimulus strength necessary to cause a response. The property of automaticity, or the ability to initiate activity, should not be confused with electrical excitability or irritability. The ability to fire spontaneously is undoubtedly distinct from the capacity to respond to a stimulus. This distinction was well recognized by Sir Thomas Lewis[9] as follows: "It is reasonable to assume that extrasystoles are due to effective impulses let loose in the muscle; [but] to assume raised excitability is not only gratuitous but is opposed by observation. The strength of the threshold stimulus may be found to be above normal in hearts which at the time exhibit spontaneous extrasystoles."

While it has long been known that delay of A-V conduction occurs following doses which do not greatly affect intraventricular conduction as judged by the duration of the QRS complex, the observation illustrated in figure 4 was quite unexpected. Due to the close proximity of the recording electrode V_1 to the stimulated point S, it would be expected that the response appearing at the point V_1 should be propagated by a path through the muscle itself. The time lapse from point S to points V_2 and V_3 must represent conduction through muscle, plus propagation through the more rapidly conducting subendocardial network, plus conduction outward from the endocardium to the surface at the respective points. The cardiac glycosides caused in every experiment an increase of conduction time to the distant points, which must include conduction through the Purkinje network, but never altered the interval between stimulus and response at the proximal ventricular electrode, which was probably attached to the same muscle unit* as the stimulating electrode and therefore was reached directly through muscle tissue. The conclusion seems inescapable that conduction over muscle tissue is not impaired by digitalis, while conduction through the fibers differentiated for rapid propagation of impulses is greatly depressed.

The action of the glycosides on conduction must play an important role in the development of ventricular fibrillation occurring as the terminal event in digitalis intoxication. It was proposed by Moe, Harris, and Wiggers[10] that electrically induced fibrillation results when a discharging ectopic focus fires at an accelerating rate into a myocardium through which conduction becomes progressively slower, with the result that the first or second of a series of beats may just have reached the remotest area of the ventricle at the moment when the second or third discharge is leaving the focus. A ventricle responding, in different areas, to two impulses at the same time is already disorganized, and can hardly escape the further complex disorganization which is fibrillation. Thus in terminal digitalis poisoning of the heart, Purkinje conduction, which is normally so rapid as to ensure activation of the whole myocardium within a short time and therefore prevent the development of alternate bands of refractory and excitable tissue, becomes depressed to the point where multiple responses are possible. This would be particularly true when the impulse-generating capacity of the myocardium is simultaneously increased.

* See Robb, J. S.: Bull. International A. M. Museums **30:** 84, 1949.

Summary

The effects of ouabain, K-strophanthoside, lanatoside C, and digitoxin on ventricular excitability and conduction velocity were compared in dogs under chloralose anesthesia. All agents caused a slight increase of ventricular excitability at dose levels of from 20 to 60 per cent of the lethal dose, followed by a decline to subnormal levels toward the end of the experiments. No significant differences between the various glycosides were observed.

All the agents caused depression of A-V conduction, terminating in complete block at about 65 per cent of the lethal dose for lanatoside C and digitoxin, and about 75 per cent of the

lethal dose for ouabain and K-strophanthoside. The slight difference was not regarded as significant.

Conduction rate within the ventricle was well maintained up to 50 to 60 per cent of the lethal dose for all the glycosides, after which progressive slowing occurred. Depression of intraventricular conduction was most marked where the conduction pathway must have included Purkinje tissue, and slight or absent between the stimulating electrodes and a close recording electrode, where the path must have been chiefly muscular.

The independence of the properties of excitability and automaticity is emphasized, and an attempt is made to interpret the induction of ventricular fibrillation by the glycosides in terms of their effects on conduction velocity and automaticity.

ACKNOWLEDGMENT

The authors wish to express their appreciation to Sandoz AG, Basel, and the Laboratoire Nativelle, Paris, for generous supplies of the glycosides used in these experiments.

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The Dye Dilution Method for Describing the Central Circulation

An Analysis of Factors Shaping the Time-Concentration Curves

By Elliot V. Newman, M.D., Margaret Merrell, Sc.D., Abraham Genecin, M.D., Carlos Monge, M.D., William R. Milnor, M.D., and William P. McKeever, M.D.

In addition to providing accurate measurement of circulation times and cardiac output, the dye dilution curves may reveal the size and location of the volumes of blood with which the dye is mixed in the central circulatory system. A trivalent approach to the analysis of these curves is presented by a combination of theoretic analysis, mechanical system experimentation and clinical observation.

THE method for measuring cardiac output based on the "dye dilution" principle of Stewart and Hamilton[1, 2] involves the injection of a known amount of colored substance into a vein and collection of serial samples of blood from an artery for determination of the concentration of dye. Other substances have been used for injection, such as salt solution and radioactive cells.[3, 4]

The validity of this method of measurement of flow depends on the assumption that the dye is distributed throughout a "central" pool of blood as it passes from the vein into the right heart chambers, the lungs, the left heart and out into the arterial system of vessels. The validity and accuracy of the method for determining rates of flow in mechanical systems and the cardiac output in animals and human subjects have been determined by other workers.[5, 6]

Our interest in the dye dilution curves has been in the theoretic and possible practical information to be derived from the shape of the curves. It was pointed out by Hamilton and others that the shape of these curves is governed not only by the flow, but also by the volume of blood in the central pool in which the dye is distributed. Previous analyses of these curves have tended to neglect the possibility that the anatomic characteristics of the pool might affect the shape of the curve, although it is obvious that, in the living organism, the central pool in which the dye is distributed is not a single volume, but a *series* of volumes made up of the veins through which the dye reaches the heart, the right heart chambers, the lung vessels, and the left heart chambers.[4, 6, 7]

The purposes of our studies are (1) to derive a theory which will describe the dye concentration change in the outflow of systems made up of series of volumes or chambers, (2) to test the theory by comparison with dilution curves obtained from mechanical models in which the flow and volumes are known and (3) to apply the theory to the dilution curves obtained on human subjects.

In setting up theoretic and mechanical systems we have started with the simplest case and proceeded to more complex models as the differences between human curves and theoretic curves suggested lines on which the assump-

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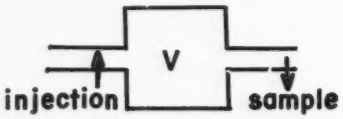
tions should be modified in order to approach more nearly the anatomic and physiologic conditions in vivo.

Case 1. The simplest system assumed was that involving a single "central pool." An equation was derived relating the concentration of dye in time in terms of the volume of the chamber and the flow through the chamber, under the following assumptions:*



(1) the injection is instantaneous into the chamber, or any mixing of the dye with fluid before entering the chamber is negligible; (2) mixing of the dye is instantaneous and complete in the chamber volume; (3) the flow and volume of fluid are constant; (4) there is no loss of dye from the system; (5) after injection only dye-free fluid flows into the system.

The formula which relates the concentration to time after injection in this single chamber system is:

$$P = \frac{M}{V} e^{-(F/V)(t-t_a)} \qquad (1)$$

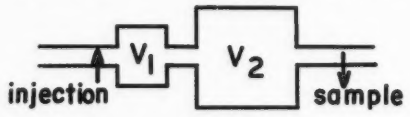
(The derivation of this and subsequent equations will be found in Appendix 2).

Figure 1 shows the results of an experiment with a model of such a "single volume" system. The points represented by dotted circles are the experimentally determined concentrations. The solid line represents the theoretic result expected from equation (1), knowing the flow and the volume of the bottle. (For details of the experimental procedure and apparatus see Appendix 1, Methods.) The agreement of the theoretic with the observed curve is evidence that our mechanical model fulfills the assumptions upon which the theory was based except for the slight duration of injection time. Since the resultant curve is a straight line on semi-logarithmic paper, and the slope, S, of the line in figure 1 is

$$S = \frac{F}{V} \qquad (1a)$$

it is apparent that it is possible to calculate the volume of the bottle in this system if one knows the flow and obtains two points on the concentration curve.

Case 2. The second step in our analysis was to derive and test the expression for the concentration of dye in the fluid flowing out of the second of two bottles in series where the first volume is smaller than the second, under the same assumptions of complete and instantaneous mixing for this two chamber system as for a single chamber. It is assumed further that no mixing takes place in the connecting tubes.



The equation relating the concentration of fluid leaving the second chamber to time is:

$$P_2 = \frac{M}{V_1 - V_2} e^{-(F/V_1)(t-t_a)} - \frac{M}{V_1 - V_2} e^{-(F/V_2)(t-t_a)} \qquad (2)$$

where V_1 and V_2 are the respective volumes of the two chambers and P_2 is the concentration in the second chamber.

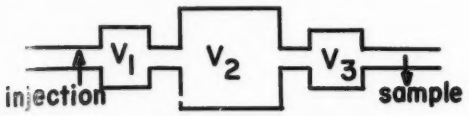
In the special case where the two volumes are equal ($V_1 = V_2$), the equation reduces to:

$$P_2 = \frac{FM}{V_1^2} (t - t_a) e^{-(F/V_1)(t-t_a)} \qquad (2a)$$

An illustration of the application of equation 2 to an experimental model is shown in figure 2. Again the theoretic curve (solid line) and the observed data (circles) agree well. It is of interest to note that when V_1 is small in proportion to V_2, the down stroke of the curve is governed only by two factors, the flow and V_2. Since in this case the first exponential term in equation 2 approaches zero rapidly, it is possible to estimate the size of V_2 from the slope of the downstroke by using equation (1a).

* In the equations which follow V = volume of chamber; F = flow through the system in terms of volume per unit of time; t = time units between injection and measurement; t_a = time at which the concentration at the sampling point corresponds to zero time at injection point; M = units of dye injected; P = concentration in volume (chamber) at time $t - t_a$ after injection.

Case 3. The third step in building a simplified model was to add a third volume in series under the same assumptions previously stated.



The equation expressing the concentration in the fluid flowing from the third bottle with time is:

$$P_3 = \frac{MV_1}{(V_1 - V_2)(V_1 - V_3)} e^{-(F/V_1)(t-t_a)} - \frac{MV_2}{(V_1 - V_2)(V_2 - V_3)} e^{-(F/V_2)(t-t_a)} + \frac{MV_3}{(V_1 - V_3)(V_2 - V_3)} e^{-(F/V_3)(t-t_a)} \quad (3)$$

where P_3 and V_3 equal respectively the concentration and the volume of the third chamber.

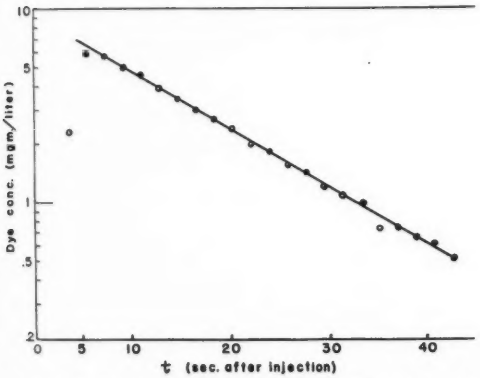


FIG. 1. Single bottle experiment. The observed dye concentration (dots) is recorded with time after a single injection of 3.97 mg. of dye into a bottle of 0.576 liter volume, with a flow through the system of 0.03917 liter per second. The solid line is determined entirely from theory (equation 1) except that it was placed on the time scale by estimating from a point on the line the value of t_a as 4.59 seconds (that is, the time at sampling site corresponding to time 0 at injection site). The rapidity with which the concentration reaches a maximum indicates the speed of the process of injection. The close fit of the theoretic line to the observed points indicates the achievement of complete mixing in the bottle.

The equation of the line is

$$P = \frac{3.97}{.576} e^{-(.0392/.576)(t-4.59)} = 9.417\, e^{-.0680t}$$

This is the general equation where V_1, V_2, and V_3 are unequal. If the system is considered analogous to that of the flow from the right side of the heart through the lungs to the left side of the heart, the special case where V_1 and V_3

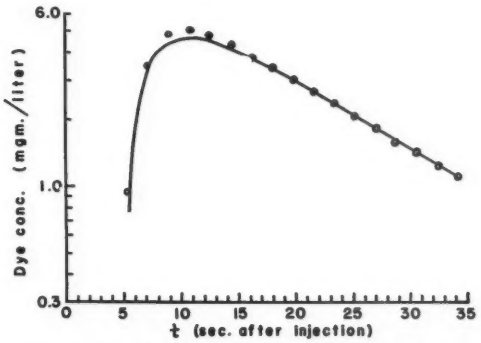


FIG. 2. Two bottle experiment. The observed dye concentration (dots) is recorded with time after a single injection of 3.93 mg. of dye into the first of two bottles in series with volumes of 0.117 and 0.570 liter respectively with a flow through the system of 0.04033 liter per second. The solid line is determined entirely from theory (equation 2) except for the value of t_a = 5.07 seconds. This was estimated by fitting the observations on the downstroke of the curve with a straight line on log paper, the slope of the line being known theoretically. The values from t = 18 through t = 34.2 were used and t_a was determined by the method of least squares. Besides the nearly exact fit of the observed data to the theory, it is noted that the effect of the small volume in series with the larger is to delay the peak concentration. The latter part of the curve, however, is entirely the same as for the single larger volume. This is explained by the fact that the dye is rapidly washed out of the small bottle so that the latter part of the curve is governed only by the size of the larger bottle (see text). Furthermore the shape of the curve is identical, whether the small bottle is before or after the larger bottle.

The slight deviation of the observed points from the theoretic curve at the peak concentration is probably due to a small amount of streaming or incomplete mixing in the smaller bottle. We have found it difficult to obtain perfect mixing in bottles under 200 cc. volume when the flow is as high as 2.42 liters per minute.

The equation of the line is

$$P_2 = -\frac{3.93}{.453} e^{-(.04033/.117)(t-5.07)} + \frac{3.93}{.453} e^{-(.04033/.570)(t-5.07)}$$

or

$$P_2 = -49.86\, e^{-.345t} + 12.42\, e^{-.071t}$$

are equal volumes would be desired. This is given by:

$$P_3 = \frac{FM}{V_1(V_1 - V_2)}(t - t_a)\, e^{-(F/V_1)(t-t_a)} - \frac{MV_2}{(V_1 - V_2)^2}\left(e^{-(F/V_1)(t-t_a)} - e^{-(F/V_2)(t-t_a)}\right) \tag{3a}$$

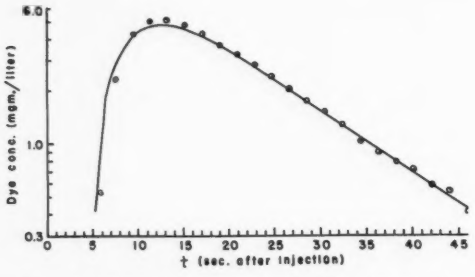


FIG. 3. Three bottle experiment. The observed dye concentration (dots) is recorded with time after a single injection of 4.80 mg. of dye into the first of three bottles in series with volumes of 0.124, 0.592, and 0.119 liters respectively with a flow through the system of 0.04833 liter per second. The solid line is obtained entirely from theory (equation 3) except for the value of $t_a = 4.38$ seconds for the observations on the straight line downstroke of the curve. This was estimated by fitting a straight line on log paper (the slope known theoretically) from 21.1 second through 46.1 second. The addition of another small bottle affects the shape of the upstroke and crown of the curve, but the slope of the downstroke line is again governed only by the volume of the largest bottle. Thus, by determining the slope of the downstroke and knowing the flow, the volume of the largest bottle can be calculated in such a system.

The equation of the line is

$$P = -254.4\, e^{-.390(t-4.38)} + 12.84\, e^{-.0817(t-4.38)} + 241.5\, e^{-.406(t-4.38)}$$

$$= -1403\, e^{-.390t} + 18.36\, e^{-.0817t} + 1430\, e^{-.406t}$$

Figure 3 shows the observed results of a model experiment for the system to which equation (3) applies, and the theoretic equation (solid line).

Again it can be seen that, if the volumes of V_1 and V_3 are small in proportion to V_2, the down stroke of the curve is governed only by the flow and volume of the largest chamber. It should be noted that these equations are valid for any sequence of the volumes. In this illustration the volumes were placed in order of small → large → small, because we were consciously seeking to imitate the normal right heart → lungs → left heart system of volumes.

To illustrate how closely the equation for three chambers in series may imitate the curves obtained on the human subject, we have illustrated in figure 4 a mechanical model and a

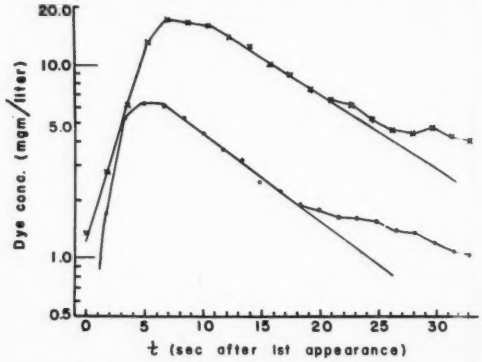


FIG. 4. Comparison of a human dye dilution curve (x) with a "model" curve (dots) shows close similarity. The flow or the cardiac output was calculated by Hamilton's method from the human curve. Using the straight line part of the downstroke of the human curve the largest volume was calculated using equation (1a) where the flow (F) is obtained from Hamilton's formula for cardiac output.

The model was then constructed with three bottles, the largest being the same volume as calculated from the human curve (550 cc.) and with the same flow. The two small bottles were arbitrarily chosen at 120 cc. in an attempt to imitate roughly the effect of the right and left heart volumes. The deviation from the straight lines at about 19 to 20 seconds is due to recirculation. In the mechanical model recirculation was accomplished by a pump which returned a fraction of the outflow from the third to the first bottle slowly enough to provide a 16 second recirculation time.

human curve. The model was constructed with V_1 and V_3 containing 120 cc. each to represent roughly the total right and left heart volumes, and with V_2 of 500 cc. to represent roughly the volume of blood in the lungs with which dye may be mixed. In order to imitate the recirculation which takes place in the human a pump was inserted after V_3 in the mechanical model, which returned a fraction of the flow back into V_1. The similarity of the two curves is obvious. The downstroke shows a sharp deviation at the point where a portion of the dye is recirculated, but it is still possible to calculate the volume

of V_2 in this case from the slope of the downstroke before recirculation.

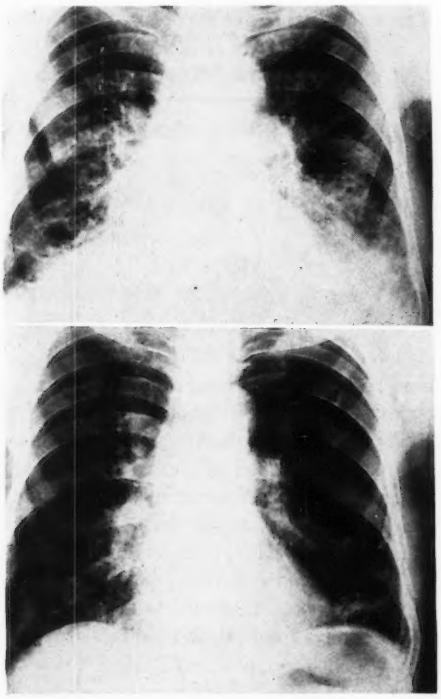


FIG. 5A

In figures 5 and 6 are illustrations of the application of the theory to a patient who recovered from cardiac failure, in whom it is reasonable to suppose that marked changes in the volume of blood in the lungs occurred. Similar calculations of the volume of blood in the pulmonary vessels in normal subjects yield a value which is in the range of magnitude suggested by

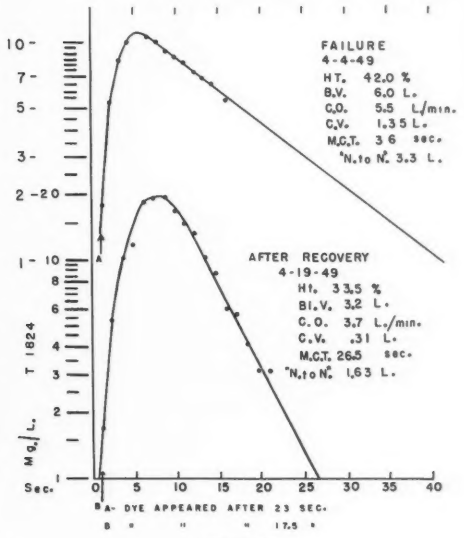


FIG. 5B

FIG. 5. The patient was a 58 year old white man. At the time of the first dye curve and chest x-ray (4/4/49) the patient was dyspneic and orthopneic with slight cyanosis. Examination of the chest showed dullness over the lower third of both lung bases and extensive loud inspiratory and expiratory rales over both lung fields particularly at the bases. He expectorated white frothy sputum. The neck veins were obviously abnormally full and the liver was enlarged and tender. There was moderate peripheral dependent edema. Pulse was 140, temperature 101 F., and respiration 48. Weight was 137 pounds. The patient was treated with bed rest, low salt diet and digitalis administration.

At the time of the second dye dilution curve and chest x-ray (4/19/49) the patient had no dyspnea or cyanosis and the neck veins emptied. The chest revealed absence of dullness at the bases and only a few scattered rales on deep inspiration just above the diaphragm. The liver was less enlarged and the weight had dropped to 109 pounds because of loss of 28 pounds of edema fluid. Temperature was 98.8 F., pulse 96 and respiration 24. Blood pressure remained between 120 to 90 systolic and 80 to 60 diastolic. The clinical diagnosis was arteriosclerotic heart disease with cardiac failure and chronic bronchitis.

The central volume ($C.V.$) was calculated from formula (1a) which relates the slope of the straight line downstroke of the curves to the flow F (or the cardiac output, $C.O.$) and to the largest volume in the chest. In this case the slope increased greatly as the patient recovered from cardiac failure and the signs of pulmonary congestion even though the cardiac output dropped. This is interpreted as being due to a marked diminution in the volume of blood in the lungs.

Ht = hematocrit, $B.V.$ = blood volume, $C.O.$ = cardiac output, $C.V.$ = central volume from formula (1a), $M.C.T.$ = mean circulation time measured from time of injection of dye, "$N.$ to $N.$" = the volume of blood calculated by multiplying the cardiac output times the mean circulation time

The ordinate is the concentration of dye (T-1824) in mg. per liter of arterial serum on a logarithmic scale. The abscissa is seconds after the appearance of the dye. In the top curve the dye first appeared 23 seconds after injection into an arm vein, and in the bottom curve, 17.5 seconds after injection.

estimates made by anatomic measurements and by estimates made from the circulation time and flow through the lungs. These results will be reported later.[8]

Case 4. One obvious discrepancy between both the mechanical and theoretic models previously considered and the human subject lies in the assumption of constant volumes within the chambers. In the contracting heart there is

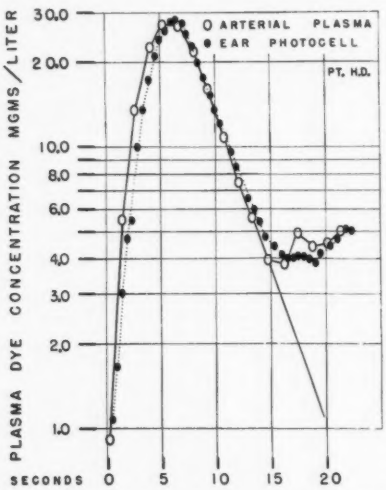
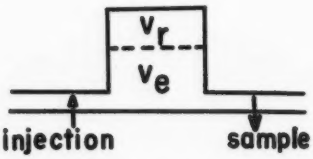


FIG. 6. Simultaneous determination of dye concentration from arterial plasma samples and from a continuous recording of the density change in the patient's ear after a single injection of T-1824 (Evans blue). This demonstrates agreement in the concentration changes from two sites in the circulation and shows no significant deviation of the serial sample method from that of continuous photoelectric recording. The circulation in patient's ear was "arterialized" by vasodilation with heat.

a changing volume with each beat. The theory next considered was for the dilution curve from a single chamber which intermittently contracts. It is assumed for this derivation that the chamber has two constant volumes, the ejection volume (V_E), and the residual volume after ejection (V_R).

Also for purposes of this analysis we assume that V_E and V_R are the same for each cycle and that there is complete mixing of the fluids in V_E and V_R before each ejection. Thus V_E plus V_R is the maximum diastolic volume of the chamber, and V_R is the volume at the end of systole.



The equation representing the concentration of dye in the outflow fluid at time t is

$$P = P_0 \left(\frac{V_R}{V_R + V_E} \right)^{\bar{F}/V_E \, t} \tag{4}$$

or

$$P = P_0 \left(\frac{V_R}{V_R + V_E} \right)^{Rt} \tag{4a}$$

where V_R is residual volume in liters; V_E is ejection volume in liters; $\bar{F}$ is total flow through the chamber or the sum of the ejection volumes in a time unit, expressed in liters per minute; R is number of ejections per minute; t is time in minutes following first ejection; P is concentration in fluid ejected from chamber in units per liter; P_0 is concentration at $t = 0$.

The slope, S, of the line obtained by plotting the logarithm of P against time is

$$S = \frac{\log P - \log P_0}{t} = R \log \left(\frac{V_R}{V_R + V_E} \right) = \frac{\bar{F}}{V} \log \left(\frac{V_R}{V_R + V_E} \right) \tag{4b}$$

The slope, S, of the concentration curve can be obtained experimentally, and V_E can be determined from an independent method of measurement of $\bar{F}$ and R (since $V_E = \frac{\bar{F}}{R}$). It is then possible to calculate the residual volume of the chamber (V_R) which is the only remaining unknown in the equation. A dye injection method for the determination of residual volume in a heart chamber is suggested by this analysis.[9]

Discussion of Assumptions Used

1. *The Assumption of Constant Volume*

A consideration of case 4 in which the contractile nature of the heart chambers is approached, makes it seem desirable to extend the three chamber theory to include this as-

sumption. It seems doubtful that the volume diluting the lungs varies greatly with each pulse and therefore equation (3) might be modified to allow for the contractile nature of V_1 and V_3. It should be noted, however, that since the downstroke of the concentration curve is determined by the largest volume in the series, and if, as seems likely in the normal, this represents the lung volume, the modification of the theory to account for the contractile nature of the heart may not affect the downstroke appreciably.

2. *The Assumption of Complete Mixing*

The theory developed made use of the assumption that the dye is completely mixed with all the fluid in each chamber. The effect upon the curve of incomplete mixing can be easily demonstrated in our mechanical model (see Appendix 1, Methods) by omitting the precautions taken to insure complete mixing, in which case the calculation of the volume of a single chamber from the formula $S = \frac{F}{V}$ gives erroneously low results. The calculation in this case represents the apparent volume with which the dye was mixed. The formation of streams of flow within the heart chambers and lung vessels might prevent complete and uniform mixing. How much error in the calculation of volumes is introduced by incomplete mixing can be determined only by experimental observations on the intact circulation. It seems likely however, that good mixing within the heart chambers does occur, since the Fick principle of flow measurement gives reproducible results from samples of "mixed venous blood" obtained from the right ventricle.[10] In mechanical models using bottles of from 100 to 1000 cc. volume the turbulence created only by the inflow is adequate to mix the dye with 85 to 95 per cent of the volume in the bottles.

It may be questioned whether the blood in the lungs can be treated theoretically as a single mixing chamber. It is obvious that the blood in the lungs is contained in a multitude of parallel channels. So long as the flow is proportional to the volume in each separate channel, the theory for a single volume will apply to the net effect of a multitude of parallel channels. How much the circulatory system of the lungs deviates from the theory in this respect remains a problem for experimental determination. An answer to this problem could be obtained by determining simultaneous dilution curves from various segments of the lung.

3. *The Assumption of Instantaneous Injection*

Experimental conditions may deviate from the theory by failure to fulfill the assumption that the injection of the dye is instantaneous. In mechanical experiments, virtually instantaneous injection can be achieved as shown by the agreement between theory and observations in the models (figs. 1, 2, 3).

However, in clinical practice the dye is usually injected into a peripheral vein and some delay in entering the right heart may occur due to mixing of the dye with blood in the veins. Precautions can be taken to minimize this delay, and the delay can be eliminated if the dye is injected into the heart through an inlying catheter. This error would in most cases affect only the first part of the dye curves but would not alter the final downstroke of the curve after all the dye had entered the lungs or the largest volume.

4. *The Assumption of No Recirculation*

The assumption that only dye-free fluid enters the system after injection of the dye is valid only until recirculation of dye occurs in the intact closed circuit. However, in most cases it may be possible to determine the constants which describe the curve before significant recirculation occurs. Recently Nylin has shown that recirculation into the right heart of man is earlier than had been previously supposed.[11]

5. *The Assumption of Constant Flow*

A variation in flow during the observation period would change the shape of the curve and impair the usefulness of the curves for the calculation of the volumes in the system.

6. *The Assumption of Representative Sampling*

Under ideal conditions the theory requires continuous recording of the concentration of

dye in the outflow fluid. While our mechanical collection system gives only successive samples, the interval between samples is so short that the error is trivial. Furthermore, comparison of dye curves obtained from human subjects by collecting consecutive two-second samples of arterial blood with curves obtained from a continuous photoelectric recording device on the ear has shown substantial agreement (fig. 7).[8]

It might be questioned whether the same curve would be obtained from all points in the peripheral arterial circulation. The identity of the simultaneous curves from two different sites supports the assumption that the concentration curve is not modified in the arterial pathways after leaving the heart.

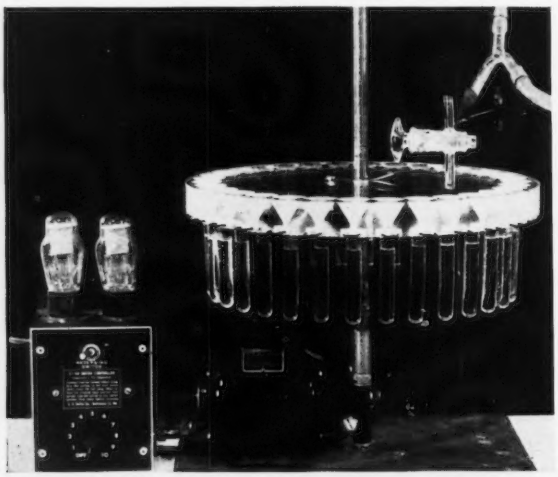


FIG. 7. The collection device for serial sampling. The rotating disk is lucite, with a rim of thirty-two contiguous funnels draining into the removable test tubes. The disk is rotated at constant speed by an electronically controlled switch and motor with a high gear ratio. The flow from the sampling side-arm (upper right hand corner), and the speed of the turntable are adjusted so that samples of 3 to 5 cc. volume are collected at one to two second intervals. The disk was designed and constructed by Mr. Lester Reynolds, Instrument Maker of the Department of Medicine.

Discussion

Our analysis of the factors shaping the dye dilution curves is meant to be used as a rational guide to interpretation and to further investigation. The validity of the theories set forth depends entirely upon the fulfillment of the assumptions by the flow system being analyzed. In the model systems the theory can be substantiated. In the human flow system proof of the validity of these theories requires further investigation, and the analysis seems valuable because it suggests experiments which will either substantiate the theory or will allow modification of the theory to fit the system. For example, it may be possible to obtain further evidence as to whether the lung volume governs the slope of the downstroke of the dilution curves. If dye is injected into a peripheral vein, the right auricle, the right ventricle and the pulmonary artery in the same individual under constant conditions of flow, the slopes of the downstrokes should be identical, if the present analysis is correct.

Besides the analysis of normal curves, there may be important and useful information to be obtained by a consideration of the effects of shunts upon the curves. We have begun preliminary observations on model systems and patients on theoretic analysis of the shape of curves obtained when shunts of different sizes, directions and locations are inserted into the system. It seems certain that accurate information concerning the size, direction, and location of intracardiac shunts may be obtained from arterial dye dilution curves.

The theory of the dilution curve obtained from contractile chambers may be useful for determining the size of the residual volume in individual chambers of the heart if one can obtain the dilution curve emerging from the chamber. Preliminary observations make it reasonable to expect that dilution curves may be obtained from isolated chambers of the heart by determining the dilution of injected radiopaque materials with a photofluorographic technic. Our experience with contractile model systems indicates that it is necessary to determine accurately the dilution of injected material which occurs with each heartbeat in order to calculate the residual volume of contractile chambers.

Summary and Conclusions

1. A theoretic analysis has been made of some factors governing the time concentration curve in flow systems made up of a series of volumes into which dye is injected, under certain fixed assumptions as to the characteristics of the flow system for one, two, and three chamber systems.

2. A technic and an apparatus are described for a rapid serial sampling from flow systems for determination of rapid concentration changes. This apparatus has been used in mechanical model experiments set up under the conditions of the flow system postulated for the theory. Agreement between the experimental and theoretic results is shown.

3. There is general similarity obtained from a three-chambered model flow system imitating roughly the right heart, lung, and left heart chambers, and curves obtained from the heart-lung flow system of the normal human subject. The extent to which the basic assumptions are fulfilled in the human subject is discussed.

4. Agreement between curves from serial arterial blood samples and from continuous photoelectric recording of dye density in the arterialized human ear is demonstrated.

5. Our analysis suggests that the time concentration curves after a single injection of dye may be used to obtain information concerning the relative size of the volumes of blood in the heart chambers and lungs and the residual volume of the heart.

Appendix 1: Methods

Mechanical Models. The models consisted of bottles connected in series to a water supply by flexible tubing. The connections between bottles were as short as possible. The inflow tube was led to the bottom of the bottle and the outflow was near the opening. In order to insure complete mixing, about 20 cc. of mercury were placed in the bottle and the system was mounted on a shaking machine. The mercury split into fine droplets which moved vigorously. That complete mixing was obtained by this method is demonstrated by the agreement between the theoretic curves and the observed curves. The outflow was led to a large calibrated container so that an accurate measure of the flow was obtained during the experiment. The dye was injected by syringe through a needle inserted into the flexible inflow tubing near the first bottle. The serial samples for determination of dye concentration were obtained from a side arm on the outflow tubing. (fig. 7). The serial samples were collected continuously by means of the illustrated rotating lucite disk into which there are drilled a continuous series of funnels of constant diameter. The disk rotated at constant speed, making possible the collection of accurately timed serial samples with no spillage of fluid, which is essential for accurate results. The concentration of dye in each tube was determined by photoelectric colorimetry. The amount of dye injected was determined by weighing the syringe before and after injection. A check on the amount of dye actually injected was obtained by collecting all the outflow fluid in a large container and determining the amount in the total flow through the system after injection.

At first we attempted to use the dye T-1824 (Evans blue) for the model experiments, but found this unsatisfactory because tap water caused an inconstant change in the color. Satisfactory colorimeter results were obtained with phenolsulfonphthalein (PSP) as the dye. The samples were alkalinized by a small drop of concentrated potassium hydroxide solution before reading.

The curves on human subjects were obtained from serial samples of arterial blood from the brachial or femoral artery collected with the same apparatus. The dye (T-1824, 10 to 20 mg. in 2 to 4 cc.) was injected as rapidly as possible into a large antecubital vein. A needle (size 16 to 19) was placed in the brachial or femoral artery and the blood flowed freely through a short (10 to 15 cm. in length) piece of flexible plastic tubing (internal diameter 0.4 cm.) into the funnels on the rotating disk (fig. 7). The end of the tubing was held in a fixed position over the center of the line of rotating funnels.

The blood samples in the test tubes were then covered and allowed to clot and the tubes centrifuged. The serum was then placed in a microcell

(0.1 to 0.3 cc. of serum) and the density of the dye read in a Beckman spectrophotometer at a wave length of 620Å.[12] A standard curve was made for each patient with known dilutions of T-1824 dye in serum obtained from the subject before the injection of dye. In this way, any interference from blank substances and possible alteration of T-1824 by the patient's blood was eliminated. Hemolysis was eliminated by coating the inside of the test tubes with silicone oil.*

The detailed description of the apparatus and method of continuous photoelectric recording of the density of T-1824 from the human ear (fig. 6) will be described elsewhere.[8] The curve in figure 6 was replotted from a curve written by a direct-writing electrocardiograph machine (Sanborn Visocardiette Model 51) coupled by suitable amplifiers to a phototube multiplier earpiece. The amplifiers are arranged so that the deflection of the writing pen is directly proportional to the concentration of T-1824. This apparatus is similar to that divised by Morgan and Sturm.[13]

Appendix 2: Derivation of Equations

1. *Equation (1) of Text.* If M units of dye are injected into a chamber of volume V_1, the rate of change in the number of units of dye, M_1, remaining in the chamber at any time, t, is dependent upon the concentration, P_1, at that time and the flow, F, under the assumptions stated in the text. Since no dye is contained in the fluid flowing in and each of the F units flowing out per unit of time contains $P_1 = \frac{M_1}{V_1}$ units of dye, the rate of change in amount of dye is given by

$$\frac{dM_1}{dt} = -\frac{FM_1}{V_1} = -FP_1 \tag{1}$$

Dividing both sides of equation (1) by V_1 gives the rate of change in concentration of dye as

$$\frac{dP_1}{dt} = -\frac{FP_1}{V_1} \tag{2}$$

which on integration gives

$$P_1 = a_1 e^{-(F/V_1)t} \tag{3}$$

where a_1 is the constant of integration.
To evaluate a_1 we have the condition that when $t = t_a$, $P_1 = \frac{M}{V_1}$, which gives

$$P_1 = \frac{M}{V_1} e^{-(F/V_1)(t-t_a)} \tag{4}$$

2. *Equations (2) and (2a) of Text.* If M_1 units of dye remain in chamber 1 at any time t, and M_2 units are in chamber 2 at this time, the rate of change in M_2 will depend on the concentration in the inflow from the first chamber, P_1, and in the outflow from the second, P_2. Since each unit of volume flowing in contains $P_1 = \frac{M_1}{V_1}$ units of dye and each unit flowing out contains $P_2 = \frac{M_2}{V_2}$ units, the net change in the amount of dye in the second chamber per time unit, which involves F volume units of flow is given by:

$$\frac{dM_2}{dt} = F\frac{M_1}{V_1} - F\frac{M_2}{V_2} \tag{5}$$

Dividing equation (5) by V_2 to get the change in concentration per unit of time, we have:

$$\frac{dP_2}{dt} = \frac{F}{V_2}P_1 - \frac{F}{V_2}P_2 \tag{6}$$

Since P_1 is not influenced by P_2 because of the direction of flow, P_1 as given by equation (4) may be substituted in equation (6), giving

$$\frac{dP_2}{dt} + \frac{F}{V_2}P_2 - \frac{FM}{V_1V_2}e^{-(F/V_1)(t-t_a)} \tag{7}$$

Integrating gives

$$P_2 = a_2 e^{-(F/V_2)t} + \frac{M}{V_1 - V_2}e^{-(F/V_1)(t-t_a)} \tag{8}$$

where a_2 is the constant of integration. Evaluating a_2 from the condition that when $t = t_a$, $P_2 = 0$ gives

$$P_2 = -\frac{M}{V_1 - V_2}e^{-(F/V_2)(t-t_a)} + \frac{M}{V_1 - V_2}e^{-(F/V_1)(t-t_a)} \tag{9}$$

In the special case where $V_1 = V_2$, equation (7) becomes:

$$\frac{dP_2}{dt} + \frac{F}{V_1}P_2 = \frac{FM}{V_1^2}e^{-(F/V_1)(t-t_a)} \tag{10}$$

Integrating and evaluating the constant of integration from the initial condition gives:

$$P_2 = \frac{FM}{V_1^2}(t - t_a)e^{-(F/V_1)(t-t_a)} \tag{11}$$

3. *Equations (3) and (3a) of Text.* The change per unit of time in the amount of dye M_3 in the third of

* General Eleteric Company, No. 9996, Schenectady, N. Y.

three chambers is determined by the inflow from the second chamber and the outflow. This is given by

$$\frac{dM_3}{dt} = F\frac{M_2}{V_2} - F\frac{M_3}{V_3} \tag{12}$$

Dividing equation (12) by V_3 to get change in concentration per unit of time gives:

$$\frac{dP_3}{dt} = \frac{F}{V_3}P_2 - \frac{F}{V_3}P_3 \tag{13}$$

Substituting for P_2 its value from equation (9), integrating and imposing the condition that $P_3 = 0$ when $t = t_a$ gives

$$P_3 = \frac{MV_1}{(V_1 - V_2)(V_1 - V_3)}e^{-(F/V_1)(t-t_a)} - \frac{MV_2}{(V_1 - V_2)(V_2 - V_3)}e^{-(F/V_2)(t-t_a)} + \frac{MV_3}{(V_1 - V_3)(V_2 - V_3)}e^{-(F/V_3)(t-t_a)} \tag{14}$$

For the special case of $V_1 = V_3$, substitution of V_1 for V_3 in equation (13), and integration, gives:

$$P_3 = \frac{M}{V_1 - V_2}\left[\frac{F}{V_1}(t - t_a) - \frac{V_2}{V_1 - V_2}\right]e^{-(F/V_1)(t-t_a)} + \frac{MV_2}{(V_1 - V_2)^2}e^{-(F/V_2)(t-t_a)} \tag{15}$$

4. *Equations (4) and (4a) of Text.* In a single contractile chamber with a fixed number of contractions, R, per unit of time and fixed residual and ejected volumes, V_R and V_E, (see assumptions stated in text) if the concentration in the fluid ejected by the first contraction is P_0, (time $t = 0$), then the concentration in the chamber following expansion and in the fluid ejected by the second contraction is:

$$P_0\left(\frac{V_R}{V_E + V_R}\right)$$

The concentration following the next expansion and therefore that of the fluid ejected by the third contraction is

$$P_0\left(\frac{V_R}{V_E + V_R}\right)^2$$

In general the concentration following each successive contraction and expansion will be diluted by the factor $\frac{V_R}{V_E + V_R}$, and the concentration in the ejected fluid at the xth ejection will be

$$P = P_0\left(\frac{V_R}{V_E + V_R}\right)^{x-1} \tag{16}$$

Expressing this concentration as a function of time units from first ejection we have

$$P = P_0\left(\frac{V_R}{V_E + V_R}\right)^{Rt} \tag{17}$$

or

$$P = P_0\left(\frac{V_R}{V_E + V_R}\right)^{F/V_E t} \tag{18}$$

Where F is the volume flowing through the system per time unit, that is the sum of the ejected volumes per time unit.

ACKNOWLEDGMENT

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Experimental Arterial Disease

I. The Reaction of the Pulmonary Artery to Minute Emboli of Blood Clot

By WILLIAM B. WARTMAN, M.D., ROBERT B. JENNINGS, M.D., AND BRYAN HUDSON, M.D.

When emboli of rabbit blood measuring 0.5 mm. in average diameter were injected into the ear vein of healthy adult male rabbits, they either became adherent to the walls of the pulmonary arteries or impacted in them. In either case an acute arteritis accompanied by endothelial proliferation regularly occurred. This process was reversible in some instances but in others was followed by organization of emboli which resulted in eccentric fibroelastic thickening of the intima or formation of fibrous intravascular bridges. Fatty degeneration, calcification, hemorrhage, and atheroma were absent. The lesions were self-limited and healed. They were not progressive.

THIS paper describes experiments which were made to study the effects produced in the pulmonary arteries by the injection of small emboli of blood clot. Most previous studies of pulmonary embolism have been so exclusively concerned with large emboli that the effects produced by minute emboli have been largely overlooked. Nevertheless, recent work suggests the possibility that organization and retraction of small emboli or thrombi may result in fibrous thickening of the arterial intima. Rokitansky[6] suggested such a theory to explain arteriosclerosis and Duguid[1] has recently restated it and described the morphologic evidence in favor of it.

In experiments designed to test the validity of this theory, Harrison[2] repeatedly injected saline suspensions of small fragments of human fibrin clots, having an average diameter of 0.5 mm., into the ear veins of rabbits. He described impaction of such emboli in the small muscular and nonmuscular branches of the pulmonary arteries followed by acute arteritis, organization and shrinking of the emboli so that eventually plaque-like scars of fibroelastic tissue formed in the intima. These experiments indicate that small emboli composed of human fibrin clots can, indeed, produce changes in the rabbit's pulmonary artery which bear some similarity to arteriosclerosis, although morphologically they are by no means identical with the lesions of that disease.

It seemed important to determine whether or not small clots of rabbit whole blood would also produce this effect, since such blood clots would not be foreign to the rabbit and would more closely resemble emboli which might possibly occur spontaneously.[9] Accordingly, the experiments herein described were performed.

EXPERIMENTAL PROCEDURE

Healthy, young, adult male rabbits were used as experimental animals. They were obtained from general laboratory stock, were housed in individual cages in air conditioned animal rooms kept at a temperature of 70 F. and fed as much Purina rabbit pellets and water as they desired.

Whole blood was obtained from the left ventricle of other rabbits and allowed to clot, after which the clot was placed in a Waring Blendor for one to two minutes. The average fragment resulting from this procedure measured 0.5 mm. and the largest 1.0 mm. in diameter. They were suspended in sterile normal saline so that the final volume of the suspension was about twice that of the blood from which the clots were obtained.

The blood clot suspension was injected into the ear veins of the experimental rabbits according to the schedule given in table 1 and afterwards they were killed at intervals with intravenous injections of Nembutal. Complete autopsies were done. The lungs were gently distended by injecting Zenker's formol solution into the bronchi and allowed to fix for about 16 hours. Blocks were cut from the periphery to the hilus of each lobe midway between the base and the apex. The blocks were embedded

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in paraffin, and sections of them were stained with hemotoxylin and eosin, periodic acid, and a combination of Weigert's and Van Giesen's stains. Selected sections were stained for iron and hemoglobin and sections cut frozen were stained for neutral fat with Sudan III.

The control group consisted of 15 healthy, male rabbits which were from the same stock, of comparable age and weight and maintained under the same conditions and at the same time as the experimental animals. Twelve of them received no treatment whatever and 3 rabbits were given four intravenous

TABLE 1.—*Experimental Data*

Rabbit number	Weight	Injection schedule cc. per week					Survival time in days after		Gross findings	Microscopic findings			
		1	2	3	4	5	Last dose	First dose		Distribution	Acute lesions	Chronic lesions	Sundry path. findings
WB1	2200	2.0	2.0				0	7	Pulmonary embolism	3+	+	0	Chronic myocarditis
WB4	2400	1.8	1.8	1.8	2.0		0	21	Pulmonary embolism	4+	+	0	Empyema—left
WB2	1935	2.0	1.5	1.5	1.8	1.5	38	70		2+	0	+	Chronic pyelonephritis
WB3	2385	2.0	1.5	2.0	1.8	1.5	38	70		0	0	0	Chronic pyelonephritis
WB11	2780	2.0*					3 min.	3 min.	Pulmonary embolism	3+	+	0	
WB13	2660	2.0*					3 min.	1	Pulmonary embolism	4+	+	0	Chronic myocarditis and bronchitis
		2.0											
		2.5											
WB8	2110	2.0*					3 min.	1	Pulmonary embolism	4+	+	0	Pulmonary edema
		2.0											
		1.5											
		2.0											
WB5	2310	1.5*					1	2		4+	+	0	
		2.0											
		1.5											
		2.0											
WB10	2420	2.0*					1	1.5	Massive pulmonary infarcts	3+	+	0	
		2.0											
		2.0											
WB6	2150	1.5*					3	4		3+	+	0	
		1.7											
		1.5											
		2.0											
WB7	1925	2.0*					7	8		2+	+	+	Chronic pyelonephritis
		2.0											
		2.0											
		2.0											
WB9	2250	2.0*					16	17		2+	0	+	
		2.0											
		2.0											
		2.0											
WB12	2460	2.0*					27	28		1+	0	+	
		2.0											
		2.0											
		2.0											
WB14	2220	2.0*					60	60		0	0	0	
		2.5											
		2.0											
		2.0											

* Injections given in 12 hr. periods.

injections of 2 cc. of normal saline at intervals of three hours in order to observe any changes which might be produced in the arterial wall by the injection of the suspension fluid used in the experiments.

Results

Control Series

Examination disclosed small perivascular granulomas in the periphery of the lungs of about 15 per cent of the untreated control animals (fig. 1). The affected vessels were small arteries or arterioles, frequently showing marked endothelial proliferation, and the exudate was composed of lymphocytes, small mononuclear cells and a few eosinophils. No evidence was found of spontaneous disease of the large and medium sized arteries. The pulmonary arteries of animals receiving repeated intravenous injections of sterile saline were entirely normal.

Experimental Series

Fourteen rabbits were used in the experiments (table 1). Ten received three or four injections of 2 cc. of the saline suspension of blood clots at intervals of two hours and 4 received injections twice weekly for as long as five weeks. The lungs were examined at intervals of three minutes to 70 days. After the injections, 9 animals were sacrificed during the first two weeks and 5 subsequently.

Gross Findings. At autopsy recent infarcts were discovered in the upper and middle lobes of the right lung of one animal dying about 36 hours after the injections. Five animals, which succumbed within a few minutes after the last injection, had large emboli in the right ventricle and main pulmonary artery. The right ventricle was markedly dilated and the lungs were moderately congested. Such large emboli were thought to have arisen from conglutination and propagation of injected emboli.

Microscopic Findings. Arterial lesions were widespread in the lungs of all animals examined during the first two weeks. They appeared within a few hours and persisted for about two weeks, after which they healed with variable amounts of scarring. For convenience of discussion, several variants of the acute lesion will be described separately, although in reality they occurred simultaneously. No vascular lesions were discovered in organs other than the lungs.

1. Impaction of Emboli without Demonstrable Alteration of the Artery. The earliest lesions were discovered in rabbit WB11, which died suddenly three minutes following a single injection of 2.0 cc. of blood clot suspension. The emboli had become impacted in both the muscular and nonmuscular arteries of all lobes. The muscular arteries appeared as though contracted in spasm about the emboli, for the internal elastic lamina was wrinkled, the endothelial cells were standing on end and the muscle fibers were short and robust. Numerous vacuoles were present both between and within the muscle fibers, the contents of which were negative for neutral fat, glycogen and mucin. One other animal, WB6, which was killed three days after the last injection, also showed impaction of emboli without other significant changes in the arteries.

2. Impaction of Emboli with Acute Arteritis. Outspoken acute arteritis of large muscular arteries was discovered in 6 of the 9 rabbits which were sacrificed within two weeks of injection. An early stage consisted of accumulation of polymorphonuclear leukocytes around the embolus in the lumen (fig. 2). In other vessels there was an acute, exudative arteritis either with or without necrosis at the site of the impaction (fig. 4). The perivascular lymphatic space was frequently distended with exudate and sometimes the neighboring lung tissue was also inflamed. Swelling and disarray of the endothelial cells were often conspicuous and occasionally were found at a distance from the embolus. Small, nonmuscular arteries were similarly affected. Frequently, mononuclear cells, which presumably came from the endothelium, migrated into the embolus. The elastica was unaltered except when medial necrosis occurred.

3. Hyperplasia of the Vascular Endothelium. Increase in size and number of the endothelial cells occurred in 8 of the 9 animals and was such a striking change that it deserves special mention. Both large and small arteries were affected. Frequently there were other evidences of acute inflammation, but this was not

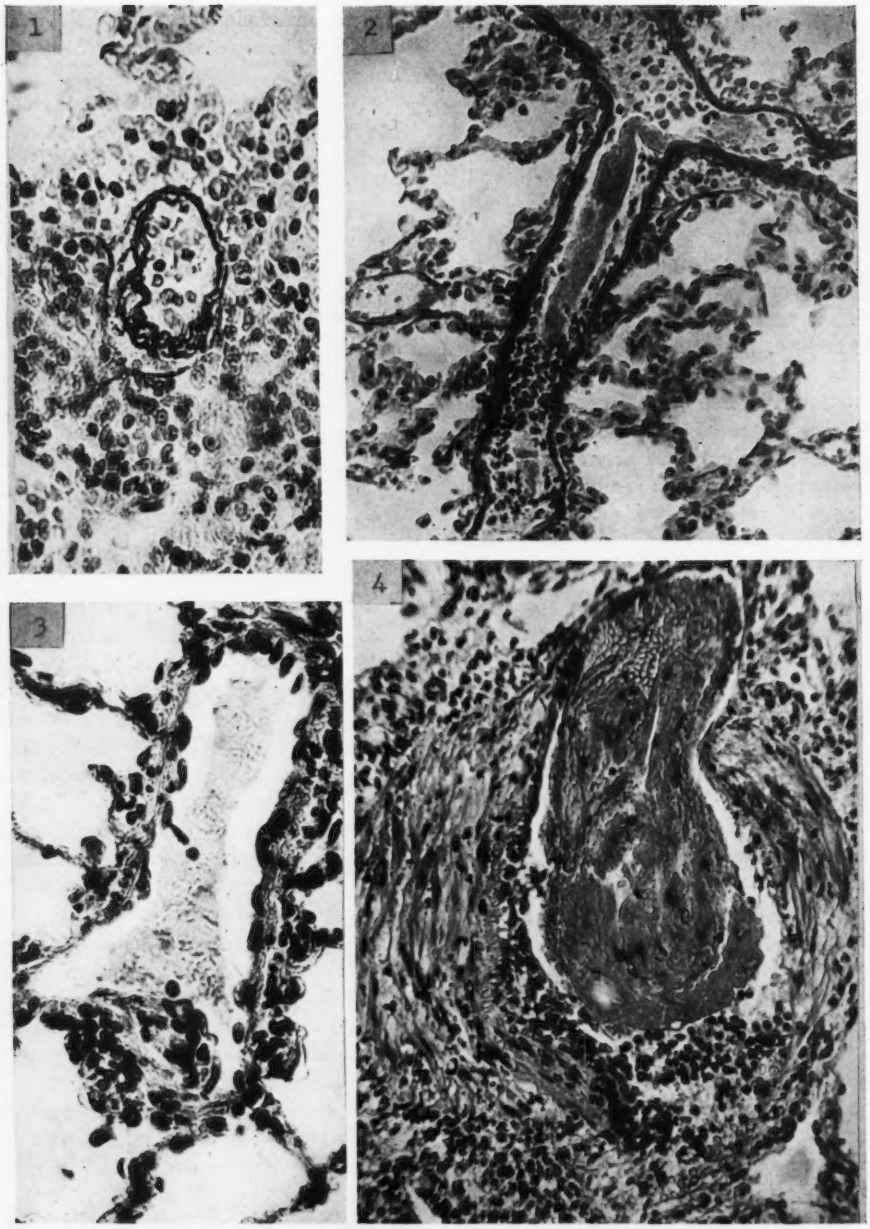


PLATE 1

FIG. 1. Control rabbit A19, right lower lobe. Small perivascular granulomas occurred in the periphery of the lungs of about 15 per cent of the control animals. The perivascular exudate is made up of mononuclear cells and a few eosinophilic leukocytes and, in addition, there is endothelial hyperplasia of the intima. Van Giesen and elastica stains, × 360.

FIG. 2. Rabbit WB1, right upper lobe. This animal died one hour after the second injection of 2 cc.

invariable and in 2 rabbits, WB6 and WB7, hyperplasia was the only discoverable evidence of vascular injury. In some cases the hyperplasia was focal and in others diffuse (figs. 3 and 5); the cells might remain in the intima or they might move into the embolus. The cytoplasm of the affected cells was swollen, granular and vacuolated, but contained no demonstrable fat, glycogen or glycoproteins. The nuclei were large and hyperchromatic and, although mitoses were not encountered, fusion of cells was observed in some of the emboli. Occasionally, especially in small arteries, the elastica did not show its specific staining properties or was fragmented. Commonly the hyperplasia was accompanied by a dense accumulation of mononuclear cells around the affected vessel.

4. Adhesion of Emboli to the Intima and Endocardium. In 2 rabbits, WB8 and WB10, emboli became adherent to the intima of large muscular arteries and formed small mural thrombi which were covered with endothelium and partly organized at the site of attachment (fig. 6). A similar emoblus was discovered adherent to the endocardium of the right ventricle of rabbit WB8. This clot was not covered with endothelium, but mononuclear cells had wandered into the base of it (fig. 7). One other instance of mural embolism has been seen in a rabbit injected intravenously with a saline suspension of small fragments of human fibrin clot and filter paper fibers and will be reported in detail in another paper.

5. Healing of the Lesions (figs. 8 to 11). The acute arteritis lasted for one to two weeks and then began to heal. The clots shrank as they became organized and covered by endothelium, and the exudate disappeared. Many arteries were completely restored to normal, but in some, focal fibrous intimal or medial scars remained to mark the site of injury. Thus, of 7 rabbits which were allowed to live for more than a week after the injections, arterial scars were found in 4. The number of arteries involved seemed to depend upon the time of examination, since after a month only a few scars remained; this suggests that the lesions were self-limiting and not progressive.

Discussion of Results

The results of these experiments are in essential agreement with those of Harrison.[2] However, since clots of blood were used in the present experiments, instead of the clots of human fibrin employed by Harrison, additional information has been obtained. Thus it has been shown that small emboli of blood clot from the same species of animal will produce lesions in the pulmonary artery which are similar to those produced by fibrin clots from a species which is foreign to the rabbit. This finding suggests the possibility that small emboli of an animal's own blood might damage the pulmonary artery. Such a possibility must, of course, remain a theory until a source for such emboli is demonstrated, which has certainly not been done in our experiments. However, the work of Knisely, Bloch, Eliot and Warner[4] on the sludging of blood indicates a possible source of such emboli and should be further investigated from this point of view.

In addition to the impaction of emboli followed by acute arteritis, organization of the emboli, and fibrous scarring of the intima, which Harrison described, the present experiments have disclosed adhesion of emboli to the intima of large vessels without impaction, and in one instance adhesion of an embolus to the endocardium of the right ventricle. Formation of bridge-like fibrous adhesions in the lumen of large branches of the pulmonary artery has also been observed. These are thought to be the

of whole rabbit blood clot suspension, or seven days after the first injection. An embolus at the bifurcation of a nonmuscular artery is surrounded by polymorphonuclear leukocytes. Van Giesen and elastica stains, × 250.

Fig. 3. Rabbit WB5, left upper lobe, one to two days after injection. Slight swelling and disarrangement of endothelial cells with a small focus of hyperphasia and perivascular exudate. Periodic acid stain, × 300.

Fig. 4. Rabbit WB1, left lower lobe (see fig. 2). An embolus impacted in a large muscular artery showing focal acute inflammation, necrosis, and perivascular exudate. Hematoxylin and eosin, × 275.

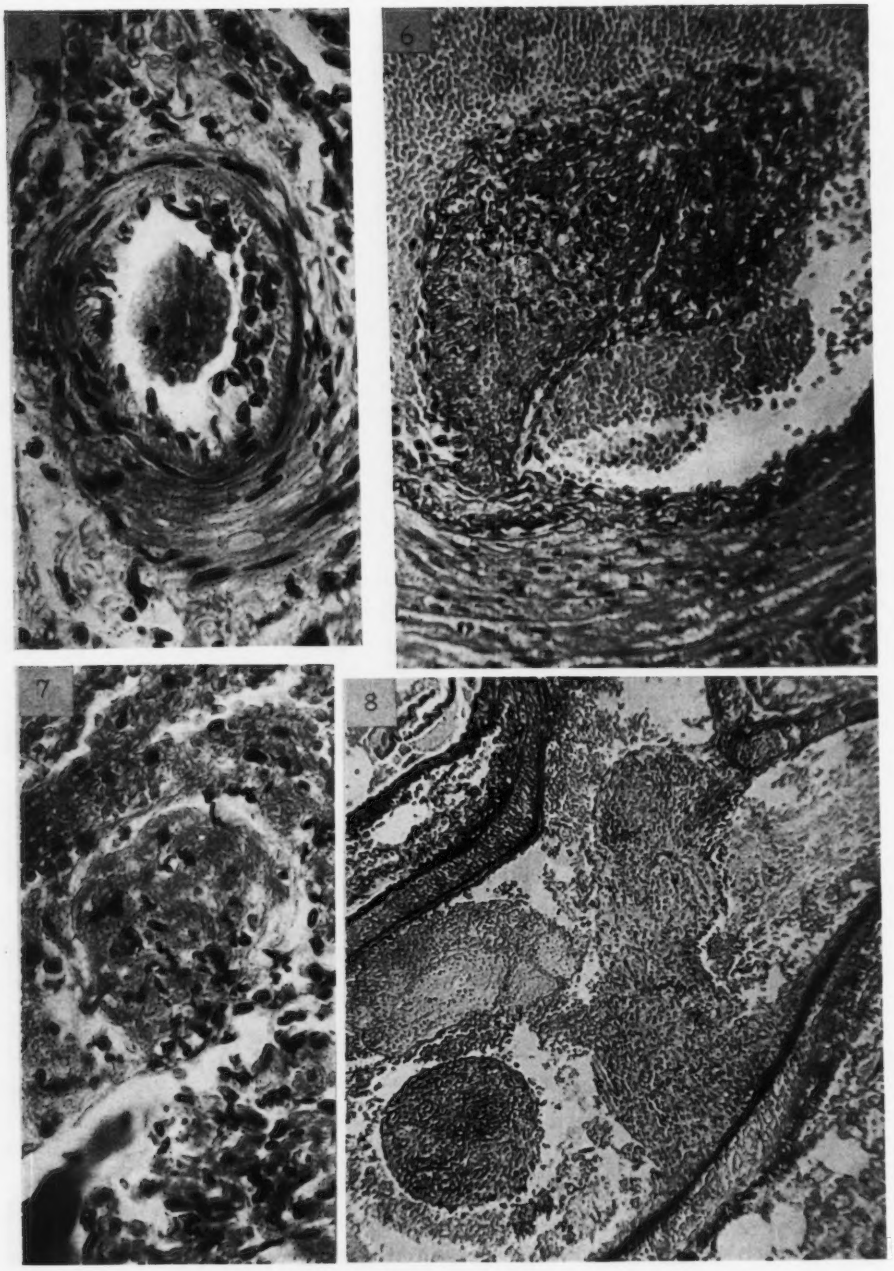


PLATE 2

FIG. 5. Rabbit WB1 (see fig. 2). Endothelial hyperplasia in a small artery with an impacted embolus. Periodic acid stain, × 300.

FIG. 6. Rabbit WB10, right middle lobe. Adhesion of an embolus to the intima of a large muscular

counterpart of the intravascular bridges which occasionally form in the human pulmonary artery as a result of thrombosis or embolism.[7]

When these experiments were undertaken it was thought that the use of blood clots instead of clots of human fibrin might lead to the production of atheromas through decomposition of the blood and that in this way lesions closely resembling spontaneous arteriosclerosis might be produced. Such, however, did not occur. Atheromas did not form, neither fat nor calcium was deposited, and hemorrhage did not occur. Only an occasional scar was vascularized and in this case the capillary walls appeared normal. These findings are in keeping with those of previously published experiments in which whole blood was injected into the media of large arteries.[8] In these experiments, too, scars and not atheromas resulted.

These experiments are of interest when considered in relation to the growing body of evidence indicating that organization of minute emboli or thrombi may lead to significant injury of either the arterial intima or of the endocardium. Mention has already been made of the observations of Duguid[1] which indicate that some forms of arteriosclerosis may possibly be causally related to organized mural thrombi. Recently Heard[3] has described a similar close association between mural thrombosis and arteriosclerosis of the renal arteries. In a study of Lambl's excresences, Magarey[5] has presented evidence which he interprets as indicating that they form as the result of the organization of partially attached deposits of fibrin on the surface of the heart valve. He also reports that "in mitral stenosis deposits of fibrin undergoing organization were found on the surface of the valve, including the angles between the cusps," and suggests that this process of organization might contribute to the progressive development of the stenosis. Thus it is apparent that there is morphologic evidence which suggests the possible importance of organization of minute emboli or thrombi in the pathogenesis of certain disorders of the cardiovascular system. The evidence that such a train of events can occur under certain experimental conditions has been set forth in the experiments described in this paper and in the paper by Harrison. However, that such a sequence of events actually does take place naturally has not been established.

Summary

The reaction of the pulmonary arteries to minute emboli of whole rabbit blood clots was studied in rabbits. It was discovered that the emboli either became impacted in the lumen or adherent to the wall of the pulmonary arteries and were there organized. During the process of organization, varying degrees of acute arteritis and endothelial hyperplasia occurred. In some arteries healing was accomplished by shrinking of the emboli and eccentric fibrous thickening of the intima. Occasionally such areas were supplied with discrete capillaries. Defects in the media were repaired by collagenous scars. Organization of emboli also resulted at times in the formation of intravascular bridges. Fatty degeneration, calcification, bleeding into the lesions or atheroma formation did not occur and there was no evidence that the lesions were progressive.

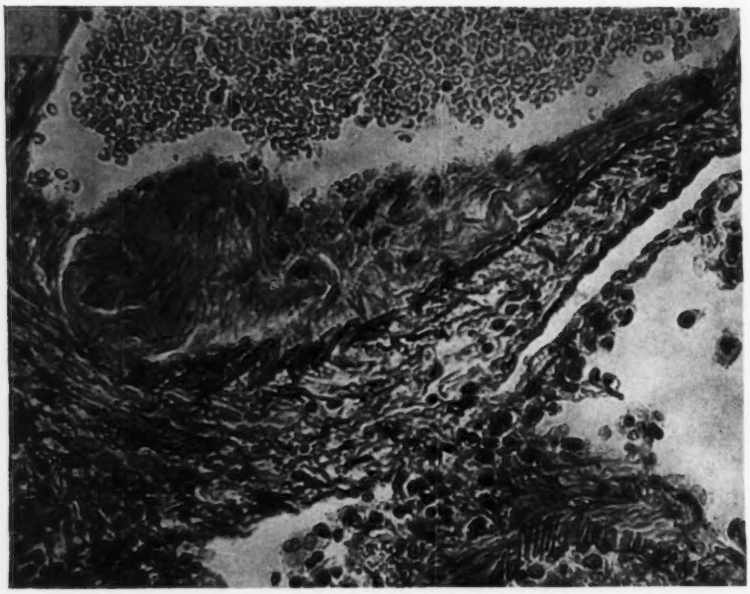
In one case an embolus became adherent to the endocardium of the right ventricle.

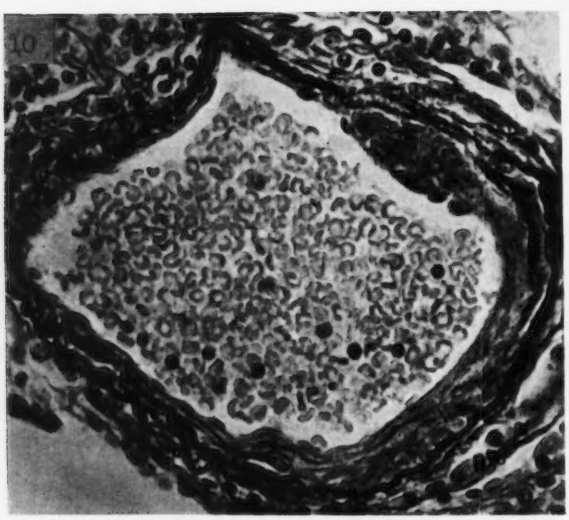
The results are discussed in the light of recent work indicating that organization of minute emboli or thrombi of blood or fibrin may contribute to the development of certain disorders of the cardiovascular system.

artery. The embolus is partly covered with a single layer of endothelial cells. Hematoxylin and eosin, × 200.

Fig. 7. Rabbit WB8, right ventricle, one day after injection. Embolus adherent to the mural endocardium. Mononuclear cells have accumulated at the site of attachment. Hematoxylin and eosin, × 275.

Fig. 8. Rabbit WB9, right upper lobe, 16 to 17 days after injection. Organization of an embolus resulting in bridge-like adhesions. Van Giesen and elastica stains, × 75.





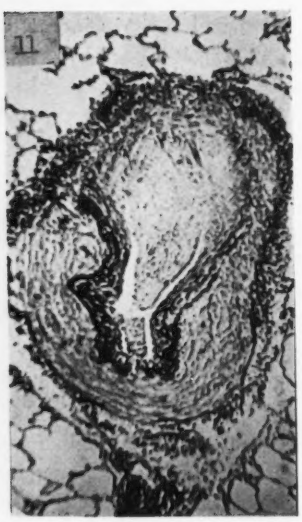


PLATE 3

FIG. 9. Rabbit WB2, right upper lobe, 38 days after the last and 70 days after the first injection. Fibrous intimal plaque in a large artery. Van Giesen and elastica stains, × 275.

FIG. 10. Rabbit WB2, right upper lobe. Fibrous intimal plaque in a small artery. Van Giesen and elastica stains, × 300.

FIG. 11. Rabbit WB4, right lower lobe, 21 days after the first injection and immediately after the last of four injections. Impaction of an embolus in a medium sized muscular artery with destruction and fibrous repair of the media and elastica. Van Giesen and elastica stains, × 100.

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Experimental Arterial Disease

II. The Reaction of the Pulmonary Artery to Emboli of Filter Paper Fibers

By William B. Wartman, M.D., Bryan Hudson, M.D., and Robert B. Jennings, M.D.

Rabbits were injected with saline suspensions of fibers of filter paper and of mixtures of filter paper and human fibrin or filter paper and rabbit whole blood. The emboli became impacted in the pulmonary arteries or adhered to the intima. In one rabbit an embolus adhered to the endocardium of the right ventricle. An acute arteritis resulted which was finally organized leaving a diffuse or eccentric scar on the intima. The filter paper fibers were surrounded by a foreign body granuloma and localized in either the intima or adventitia. Frequently they passed entirely through the wall causing varying amounts of injury and were found in the adventitia or perivascular lung tissue. This is interpreted as indicating the existence of a mechanism for ridding the circulation of foreign material in the blood.

In a previous paper the reaction of the pulmonary artery to the presence of minute emboli of whole blood has been described.[5] This paper presents the results of experiments which were made in order to study the reaction of the pulmonary artery to different kinds of emboli, namely small fibers of filter paper and mixtures of filter paper and either rabbit's blood or human fibrin.

Experimental Procedure

Healthy, young, adult, white rabbits from general laboratory stock were used in the experiments. They were housed in individual cages in air-conditioned animal rooms kept at 70 F. and were fed as much Purina rabbit pellets and water as they desired. Untreated control rabbits were maintained simultaneously and under the same conditions as the experimental animals.

Suspensions of sterile filter paper were prepared by cutting a square centimeter piece of Whatman No. 3 paper* into fine pieces with scissors and placing them in a Waring Blendor with 50 cc. of physiologic saline solution for two minutes. This treatment separated the individual fibers and broke them into fragments measuring approximately 10 by 80 microns.

Mixtures of human fibrin and filter paper were prepared by allowing freshly drawn whole blood to clot. After freeing the clot of serum it was broken into small pieces by agitation with glass beads and washed with normal saline on Whatman No. 3 filter paper. The clot was then suspended in saline, shaken with glass beads, and refiltered, the whole process being repeated until the final fibrin clot was grossly free of blood. It was suspended in an amount of normal saline which was slightly less than the original volume of blood from which the fibrin was obtained. Enough filter paper fibers became enmeshed in the clot during the process of preparation to suffice for the purposes of the experiments.

Mixtures of whole rabbit blood were prepared as described previously[5] and then mixed with the suspension of filter paper.

In order to obtain suspensions of pure human fibrin, glass wool was substituted for filter paper and after removal of red blood cells the clot was fragmented in a Waring Blendor in 50 cc. of normal saline for two minutes. The average size of the particles obtained in this way was 0.1 mm.

Injections of the different suspensions were made into the ear veins and the animals were sacrificed at selected intervals according to the schedule shown in table 1. Autopsies were performed and sections of lungs and other organs prepared as in previous experiments.[5]

Results

In about 15 per cent of the control rabbits small granulomas were found around a few of the end branches of the pulmonary arteries. Since these lesions have been described and illustrated in a previous article they will not be discussed further. Suffice it to say that no le-

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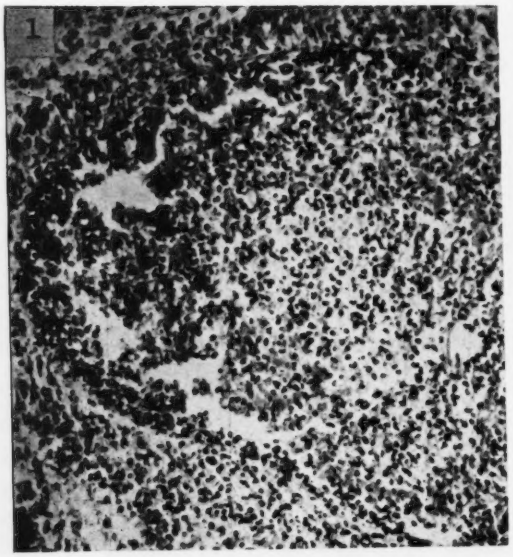
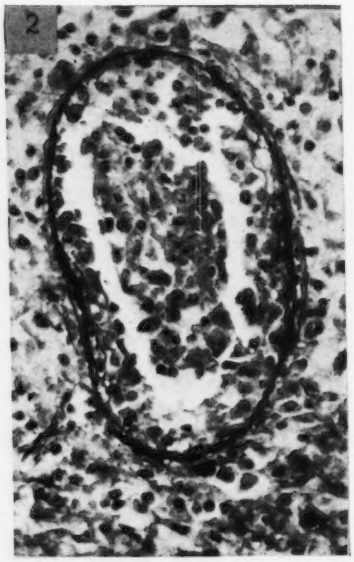
* This paper is made of cotton fibers and a negligible quantity of linen.

TABLE 1.—*Experimental Data*

Rabbit number	Material injected	Weekly schedule of intravenous injections in cc.								Survival after injections in days		Acute lesions	Chronic lesions
		1	2	3	4	5	6	7	8	Last	First		
FP1	Filter paper	1.5	1.5							0	7	2+	0
FP	Filter paper	1.5	1.5	1.5						14	28	0	4+
FP2	Filter paper	1.5	1.5							39	53	0	2+
FP	Filter paper	1.5	1.5							78	92	0	3+
FP5	Filter paper	1.5	1.5							157	164	0	2+
A1	Fibrin	1.5											
	Filter paper	1.5	1.5			2.0				1	29	2+	3+
A8	Fibrin		0.8										
	Filter paper	1.0	1.5	2.0			1.8			2	37	3+	3+
A7	Fibrin		0.9										
	Filter paper	1.2	0.8	1.8		0.5				16	47	0	3+
A2	Fibrin		1.0										
	Filter paper	1.0	2.0	1.0			1.5			18	53	0	2+
A6	Fibrin		2.0										
	Filter paper	1.2	1.0	2.0			1.5			26	61	0	2+
A5	Fibrin		0.8										
	Filter paper	1.0	2.0	1.8			1.5			39	74	0	4+
A3	Fibrin												
	Filter paper	1.5	1.0				2.0			46	81	0	3+
A9	Fibrin		2.0										
	Filter paper	1.5	1.8	1.5			2.0			54	88	0	3+
A4	Fibrin		1.0										
	Filter paper	1.5	2.0	1.5			1.2			63	95	0	2+
A10	Fibrin		0.5										
	Filter paper	2.0	1.5	1.5						88	102	0	1+
A16	Rabbit blood	8.0*								1	1	3+	0
	Filter paper	8.0											
		8.0											
A17	Rabbit blood	10.0*								34	34	0	2+
	Filter paper	10.0											
		10.0											
A14	Rabbit blood	6.0								47	47	0	3+
	Filter paper												
A15	Rabbit blood	5.0								47	47	0	0
	Filter paper												
F6	Human fibrin	2.0*								1	2	0	0
		2.0											
		2.0											
		2.0											
F7	Human fibrin	2.0								4	5	0	0
		1.8											
		1.8											
		2.0											
F8	Human fibrin	2.0								7	8	0	0
		1.5											
		2.0											
		1.5											
F3	Human fibrin	2.6	2.6			1.8		1.5	1.5	10	63	0	1+
F2	Human fibrin	2.0	2.0			1.0				14	44	0	±
F1	Human fibrin	1.8	2.2			1.0				14	44	0	0
F4	Human fibrin	2.0	1.6			1.3		1.5	1.5	21	75	0	0
F5	Human fibrin	2.0	2.0			1.8		1.5	1.5	21	75	0	0

* Given in a 12 hour period.





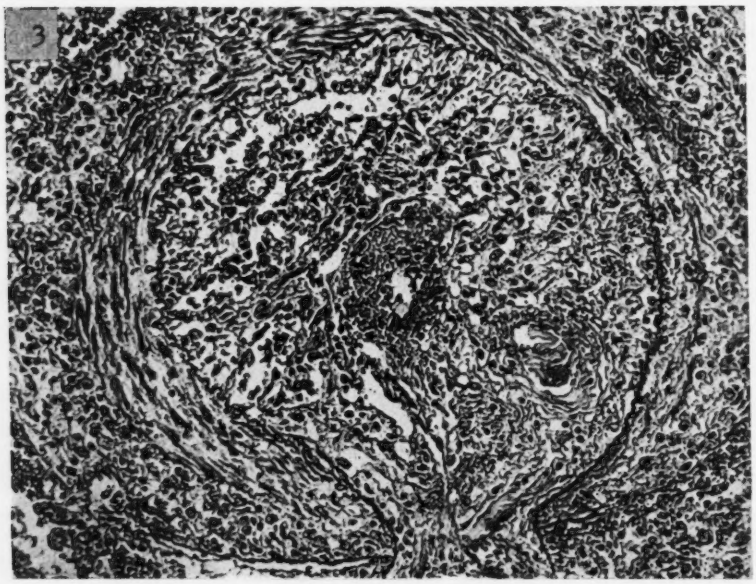


FIG. 1. Rabbit A8. Acute necrotizing arteritis two days after the last of five injections of a mixture of filter paper and human fibrin clot. Hematoxylin and eosin, × 120.

FIG. 2. Rabbit A8. (See fig. 1.) Endothelial proliferation and perivascular exudation of mononuclear cells in a small artery. Van Giesen and elastica stains, × 240.

FIG. 3. Rabbit A8. (See fig. 1.) Impaction of an embolus in a large artery with organizing acute inflammation. Periodic acid stain, × 220.

sions resembling those about to be described in the experimental animals were discovered in the controls.

Since the same changes were produced by the injection of either pure filter paper fibers, or of mixtures of filter paper fibers and fibrin or

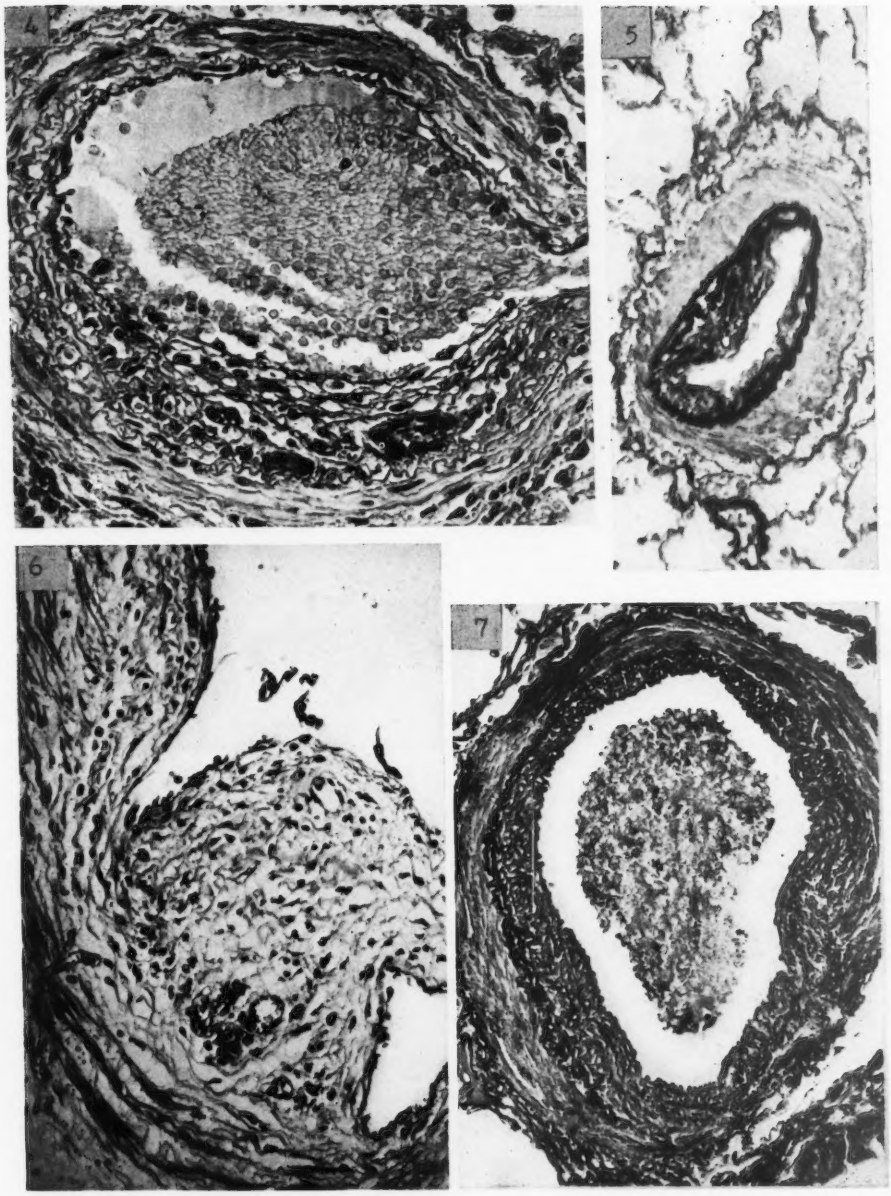


FIG. 4. Rabbit FP3. Chronic inflammation of the intima following injection of minute emboli of filter paper fibers. Age range 78 to 92 days. The giant cell contains a fiber. Periodic acid stain, × 300.

FIG. 5. Rabbit A9. Fibroelastic intimal scarring of a small muscular artery 54 to 88 days after the injection of human fibrin clots containing filter paper fibers. Van Giesen and elastica stains, × 360.

FIG. 6. Rabbit A8. Eccentric fibrous thickening of the intima in a large artery. Several capillaries are present including one in the lower left hand corner which extends from the adventitia into the intima. Hematoxylin and eosin, × 360.

FIG. 7. Rabbit A5. Diffuse fibroelastic thickening of the intima following repeated injection of a mixture of human fibrin and filter paper fibers. Age range 39 to 74 days. Van Giesen and elastica stains, × 120.

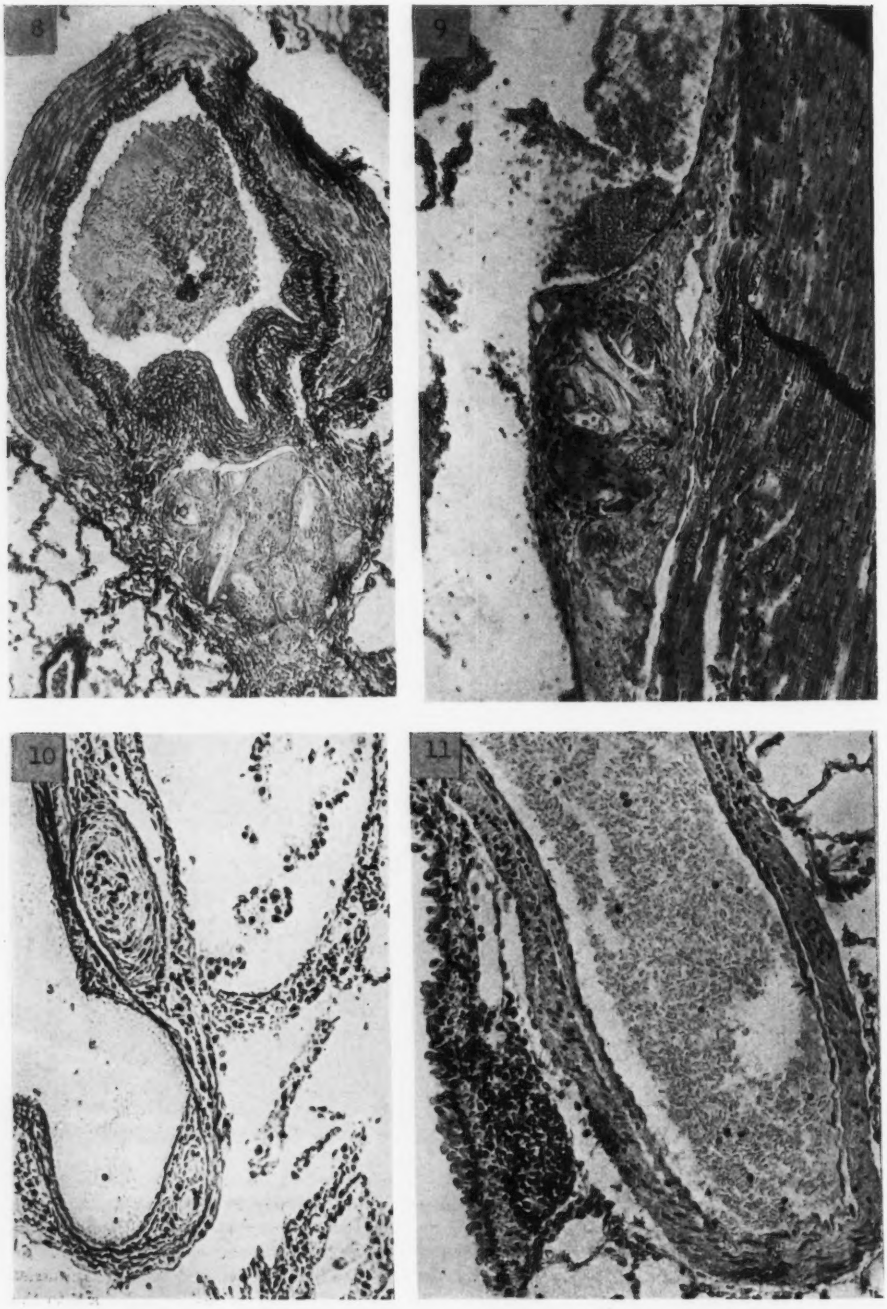


FIG. 8. Rabbit A8. (See fig. 6.) Passage of filter paper fibers through the wall of a large muscular artery with destruction of all coats and replacement fibrosis of intima and media. The fibers are surrounded by a foreign body type of granuloma which is rich in multinucleated giant cells. Age

whole blood, they will be described together. Animals which received injections of human fibrin without filter paper will be described separately, as the results were different.

Four rabbits were examined at intervals of a few minutes to seven days after the last injection and all showed widespread impaction or adhesion of emboli with moderate to marked acute arteritis (table 1, animals FP4, A1, A8, A15). These changes are illustrated in figures 1 to 3 and are identical with those produced by the injection of minute emboli of whole rabbit blood clots except that they are more severe. No animal which was examined within the first few days failed to show these lesions.

After a week or ten days the acute lesions became organized. Fibroblasts, a few capillaries and mononuclear phagocytes appeared and the clot retracted, and became endothelialized, forming an eccentric plaque on the intima. Within the space of several weeks the process of organization had resulted in fibroelastic scarring of the intima of a considerable number of both large and small arteries (figs. 4 to 8). In 2 animals fibrous bridges formed in the lumens of large arteries. Chronic or healed lesions were observed in 16 of 17 rabbits and as long as 157 days after the last injection or 164 days after the first (table 1). They were similar to those discovered after the injection of clots of rabbit whole blood but occurred in a higher percentage of animals and were more marked. As in the case of the blood clot injections, the finding of arteries which showed no evidence of chronic lesions was interpreted as indicating that many acute lesions healed completely.

It has been shown previously[5] that not only may blood clot emboli become impacted in the pulmonary arteries, but some of them may adhere to the arterial intima or even to the endocardium of the right ventricle. In these experiments, likewise, adhesion of emboli both to the intima and to the endocardium of the right ventricle has been encountered (fig. 9).

Of especial interest was the behavior of the filter paper fibers. In the main they caused a foreign body type of inflammatory reaction. Some were engulfed by foreign body giant cells and embedded in the intima in dense plaques of avascular collagenous tissue, whereas others were located in the media or adventitia. It was quite clear that the fibers could either pass entirely through the arterial wall or stop anywhere along the way. It was also equally clear that this was accomplished with varying amounts of injury to the artery and at times without visible evidence of injury of any kind (figs. 8, 10).

The results of injecting minute clots of human fibrin were negative (table 1). Of 3 rabbits receiving four injections of 2 cc. each during a period of 24 hours, none showed acute lesions during the first week. Of 5 rabbits which received multiple intravenous injections for as long as eight weeks, 3 showed no lesions whatever and 2 showed very slight intimal thickening and endothelial hyperplasia in a few small arteries. Nothing resembling the lesions produced by injection of a mixture of human fibrin and filter paper fibers was seen.

Discussion of the Results

Similar changes in the pulmonary arteries have been described by Von Glahn and Hall[4] following the injection of small cotton fibers into the iliac veins of rats, and by Flory[1] after injection of material from the atheromatous plaques of patients with arteriosclerosis. Von

range 2 to 37 days. Rabbit injected with a mixture of human fibrin and filter paper. Van Giesen and elastica stains, × 120.

Fig. 9. Rabbit A1. Embolus of human fibrin and filter paper adherent to the endocardium of the right ventricle. Organization is well advanced and the fibers of filter paper have been phagocytosed by multinucleated giant cells. A single layer of endothelium covers the embolus. The rabbit was killed 29 days after the first injection of a mixture of rabbit fibrin and filter paper or one day after the last injection. Hematoxylin and eosin, × 300.

Fig. 10. Rabbit FP3. (See fig. 4.) A small fibrous intimal plaque at the site of adhesion of a filter paper fiber is present in the lower right hand corner. Another fiber surrounded by a healed granuloma is present in the lymphatic between the artery and bronchus. Van Giesen and elastica stains, × 120.

Fig. 11. Rabbit S2. A control animal showing a lymphatic vessel lying between an artery and a bronchus with a small nodule of lymphocytes at the lower end. Hematoxylin and eosin, × 150.

Glahn and Hall were led to perform their experiments because they had discovered foreign body granulomas in the pulmonary arteries of 6 patients who had received recent intravenous injections of saline filtered through cotton or from flasks stoppered with cotton plugs which had adhered to the mouth of the flask. Konwaler[3] has reported finding similar foreign body granulomas in the pulmonary arteries of 2 other patients who had received intravenous injections of fluids. Von Glahn and Hall and Flory described repair of the lesions within a period of six months and did not observe chronic or healed lesions of the type seen in our animals. Adhesion of the emboli to the arterial wall or to the endocardium of the right ventricle was also not described. The lesions also are essentially similar to those obtained by Harrison[2] when he injected finely fragmented clots of human fibrin, and by Wartman, Jennings and Hudson[5] who injected minute emboli of rabbit blood clots. The results of these experiments and their bearing on certain morphologic observations, which indicate that organization of small emboli may be a factor in the development of Lambl's excresences and of certain forms of arteriosclerosis and progressive mitral stenosis, have been discussed elsewhere.[5]

The results of the present experiments indicate that foreign bodies, such as filter paper fibers, provided they gain access to the circulation, may become impacted or adherent in the pulmonary arteries and produce an intense acute arteritis. As the arteritis heals the emboli become organized and shrink, leaving in some instances plaque-like fibroelastic scars of the intima, media, or adventitia. Thus the injection of even minute foreign bodies may be fraught with serious consequences and great care should be taken in the preparation of solutions or materials for intravenous injection in order to make certain that they do not contain foreign substances.

Of considerable theoretic interest is the demonstration that a mechanism exists by means of which emboli such as filter paper fibers may be cleared from the circulation in the lungs. This is indicated by the finding of the fibers not only within the wall of arteries but also in the adventitia and perivascular tissues. Obviously such fibers must have passed through the arterial wall, but just how this was accomplished was not made clear by these experiments. Either the fiber could be pushed through the wall and then engulfed by phagocytes, or it could be first phagocytosed and then carried through the vessel by the phagocyte. This process frequently resulted in injury of the affected artery, but occasionally occurred without demonstrable permanent damage.

Some insight into the mechanism for clearing foreign material from the blood stream was gained from an examination of arteries which lie adjacent to bronchi. It became apparent from examination of sections from the lungs of control animals that there was often a nodule of lymphoid tissue lying between the artery and the bronchus. These lymphoid nodules varied greatly in size, and in the small ones it was always possible to identify a lymphatic lying between the artery and bronchus from which the lymphoid nodule arose (fig. 11). In the experimental animals it was also noted that filter paper fibers and the accompanying granuloma were frequently in the same situation ((fig. 10). Thus it seems likely that in this particular situation the foreign material, after clearing the artery, passed into this lymphatic and then, depending upon its size, was either removed or localized in this place. The possibility also exists that the foreign body could pass from the lymphatic into the bronchus and be coughed up, but this has not been observed. It may well be that the lymphoid nodules seen in this location in control rabbits are due to some such mechanism.

The failure to produce arterial lesions by the injection of clots of human fibrin deserves comment because of the fact that Harrison[2] was able to produce lesions in this fashion as is proved by his excellent photomicrographs. Our experimental technic differed from Harrison's in several respects, and it may be that the differences in results are due to this. In the first place the fibrin emboli which we injected measured on the average 0.1 mm. with a maximum diameter of 0.25 mm., whereas Harrison injected much larger emboli which had an average diameter of 1 to 2 mm. This suggests the possibility that the size of the embolus may be a

factor in determining the outcome and this possibility is now being explored. In the second place our acute experiments were performed by giving four injections at intervals of a few hours in a 24 hour period in order to obtain accurately dated lesions. Harrison, in contrast, injected his animals weekly for several weeks. But this procedure was followed in our chronic experiments and no significant lesions were discovered.

Summary

Rabbits were given injections into the ear veins of saline suspensions of minute fibers of filter paper and of mixtures of filter paper and human fibrin or filter paper and rabbit whole blood clot. The emboli either became impacted in the pulmonary arteries or adhered to the intima. In one rabbit an embolus adhered to the endocardium of the right ventricle. An acute inflammation resulted which subsided after about a week. Organization of the embolus and inflamed arterial wall resulted in retraction of the embolus and diffuse or eccentric scarring of the intima. Vascularization of some of the scars was observed, but hemorrhage and deposition of lipoids were not seen. Intravascular bridges occasionally formed.

The filter paper fibers were soon surrounded by a foreign body granuloma and became localized in either the intima, media, or adventitia. They frequently passed entirely through the wall of the affected artery, causing varying amounts of injury, and were found in the adventitia or perivascular lung tissue. This is interpreted as indicating the existence of a mechanism for ridding the circulation of foreign material in the blood. Localization of the fibers in lymphatics situated between the bronchi and arteries is described. Injection of minute emboli of clots of human fibrin having an average diameter of 0.1 mm. did not cause similar lesions. This failure, which is at variance with previously reported work, may be explained by the use of extremely small emboli and a different experimental technic.

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The Management of Acute Cardiac Emergencies

By CLARENCE E. DE LA CHAPELLE, M.D., AND O. ALAN ROSE, M.D.

ALTHOUGH the majority of emergencies of cardiac origin occur in patients with structural heart disease, many involve individuals without demonstrable organic lesions. Those affecting the latter are usually due to changes in rhythm. The most common of these are the paroxysmal supraventricular tachycardias.

Most cardiac emergencies are readily diagnosed by bedside examination, but occasionally, and especially in the presence of arrhythmias, the use of precision records such as the electrocardiogram is necessary to make an accurate diagnosis. It is, of course, essential to interpret correctly the nature of any emergency in order to institute proper treatment. In this article the methods used in recognizing the various emergencies will not be stressed and only the therapeutic procedures employed in their management will be discussed.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIAS

Auricular Tachycardia

This is the most common of all paroxysmal tachycardias and occurs most often in individuals who are free from structural heart disease. In such patients the paroxysms are usually of short duration and require little or no therapy. Despite the benign nature of these episodes, medical help is not infrequently sought, especially during the initial attacks, or for paroxysms which do not respond to simple measures which most patients learn to use after experiencing repeated attacks. Among the latter are the Valsalva procedure of attempted forced expiration with the glottis shut, prolonged holding of the breath, compression of the neck, and the assumption of various positions, such as lowering the head over the side of a couch, or twisting the head in extreme rotation to either side. Lastly, patients often induce vomiting by mechanical irritation of the pharynx or by drinking mustard diluted in water.

Although death is uncommon in adults during auricular paroxysmal tachycardia, even when organic heart disease is present, serious complications, including heart failure, may occasionally ensue. In infants and young children, however, heart failure and death may occur in the absence of recognizable heart disease. When structural heart disease is present, symptoms including dyspnea, substernal pain, vertigo and syncope may result. Persistence of this rapid arrhythmia may produce heart failure. In such circumstances it is imperative that the impaired heart be spared the excessive burden of the tachycardia by abolishing the abnormal mechanism as soon as possible.

Since most patients with paroxysmal tachycardia suffer from considerable apprehension during an attack, especially during the initial episodes, a sedative in the form of a rapidly acting barbiturate should be administered as promptly as possible. The patient should be placed at rest and reassured of the innocence of the attack. These measures alone will frequently produce reversion to normal rhythm.

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As a rule morphine and other opiates are contraindicated because of the danger of possible habituation. This is particularly true if the patient does not have underlying heart disease.

If the paroxysm still persists then other methods of therapy should be used. Among these are several physical procedures. Carotid sinus pressure is the one most often tried, and probably the most successful in abolishing paroxysmal tachycardia of auricular and nodal origin. Carotid pressure is most likely to be effective if the sinuses are massaged, trying first the right and then the left. This is best performed by pressing against the carotid sinus at the angle of the jaw, compressing the carotid posteriorly and medially against the vertebral bodies. Considerable pressure in the massaging is required. If this measure is not successful before medication, it is frequently effective in converting supraventricular tachycardias after the patient has been treated with one of the drugs which produce vagal stimulation. The latter include the digitalis substances and Mecholyl. Their uses will be described below. Ocular pressure is also a physical measure to produce vagal stimulation. It is not as effective and apparently is now less often used than carotid sinus massage. Occasionally damage to the eye may result from this treatment.

Although quinidine still seems to be the drug preferred by many clinicians to terminate auricular and nodal paroxysmal tachycardias, one of the rapidly acting glycosides of digitalis is being used more frequently as the drug of choice.[1] In infants and young children who become critically ill in the presence of auricular paroxysmal tachycardias, intravenous administration of a digitalis preparation is not only effective but may actually be life-saving. Digitalis may be given by mouth in the usual digitalizing dosage if there is no urgency.

Ouabain, given intravenously, is probably the best preparation for the rapid conversion of auricular or nodal paroxysmal tachycardia. There is danger in employing this, or any other digitalis preparation, if the patient has received digitalis within the previous two weeks. The initial dose for adults is 0.5 mg. followed every hour by 0.1 mg. until the paroxysm ceases or a total of 1.0 mg. has been administered. Most patients obtain full therapeutic effect with 0.8 mg. of ouabain.

If ouabain is not available, lanatoside C (Cedilanid) may be administered intravenously.[2] The initial dose is 0.8 mg., followed by 0.4 mg. if no favorable response is obtained in one hour. The majority of patients will respond to the initial dose of 0.8 mg. However, a total of 1.6 mg. of lanatoside C may be required. Digoxin,[3] also given intravenously, is another preparation which may be employed for rapid digitalization in the management of auricular and nodal paroxysmal tachycardias. When administered intravenously the introductory dose of 0.5 mg. is followed every two hours by 0.25 mg. until full effect is obtained, or until a total of 1.5 mg. has been given.

Recently another digitalis-like substance, acetyl strophanthidin, has aroused interest but mainly from an experimental standpoint. Apparently this drug, when given intravenously, "causes an almost immediate effect on the ventricular rate of auricular fibrillation."[4] Based on clinical work reported to date, it may prove to be of value in the treatment of acute left ventricular failure, where speed is essential, and in the management of auricular paroxysmal tachycardia. At present, there is not sufficient clinical experience to warrant accurate conclusions as to the indications or value of this drug.

Quinidine, while probably less effective than digitalis, is still preferred by many physicians, at least for preliminary trial, in the treatment of supraventricular tachycardia. When using this drug it is wise to give a test dose of 0.2 Gm. to rule out an idiosyncrasy, although true allergic reactions to quinidine are rarely encountered.[5] After waiting one hour, quinidine sulfate, in doses of 0.4 Gm. to 0.6 Gm., should be given orally every two or three hours for five doses. If the attack has not terminated with this schedule of administration, increased dosages of 0.8 Gm. or 1.0 Gm. may be used in a similar manner for subsequent trials. If conversion has not occurred at these high levels it is best to discontinue quinidine, as success is unlikely. Procaine amide (Pronestyl) may be effective in the conversion of this arrhythmia. The

use and dosage of this drug will be discussed below under the treatment of ventricular tachycardia.

Another medication which is effective in the management of this arrhythmia is Mecholyl chloride (acetyl-beta-methylcholine chloride). It is given subcutaneously in doses of 20 to 40 mg. However, relatively few physicians use it because of the rather severe and unpleasant side reactions which invariably occur after the administration of this drug. Its use may be dangerous and is therefore contraindicated in the presence of allergic asthma, anginal syndrome, and following myocardial infarction. It should never be given unless atropine is available for immediate intravenous use in the event that serious reactions occur. Mecholyl must be administered only *subcutaneously* and furthermore, because of the fall in blood pressure along with other untoward effects, Mecholyl should be given with the patient in the recumbent position.

If unsuccessful alone, the above mentioned drugs are frequently effective if carotid pressure or other vagal stimulation is applied fifteen minutes to one-half hour after the medications have been given.

A number of therapeutic agents have been recommended for the treatment of paroxysmal tachycardias. None has proved to be superior to those which have been discussed. An old-fashioned remedy is used by many practitioners; namely syrup of ipecac in doses of 4 to 8 cc. This will frequently abolish supraventricular tachycardias because of the vagal effect of inducing nausea and vomiting.

Paroxysmal Auricular Fibrillation

Although this arrhythmia may occur in normal individuals it is most commonly observed in the presence of organic heart disease. The transient or paroxysmal type of auricular fibrillation is usually benign and may occur without the patient's awareness. This is especially true when there are no structural changes in the heart. Paroxysmal auricular fibrillation is a relatively common complication of hyperthyroidism and acute infections, such as pneumonia, even in the absence of structural heart changes. In patients with organic heart disease, including those with rheumatic carditis, fibrillation may precipitate acute heart failure or embolization. It therefore requires emergency treatment.

As with paroxysmal tachycardia, the initial treatment should include physical and mental rest obtained by means of a sedative, preferably a barbituric acid derivative. Morphine may be required in those patients with organic heart disease in whom heart failure may be precipitated by the arrhythmia.

Quinidine is usually effective in converting paroxysmal auricular fibrillation to normal sinus rhythm, and is considered by most clinicians to be the drug of choice for this purpose, regardless of the underlying type of heart disease. However, in the presence of a recent myocardial infarct, caution must be exercised in the use of quinidine, particularly if heart failure or embolism has occurred. There is no doubt that anticoagulant therapy has made this problem somewhat easier, since, with this treatment, the tendency for the deposition of mural thrombi and therefore of embolism can probably be diminished. Most clinicians digitalize patients who show signs of heart failure or who have a rapid ventricular rate as a result of auricular fibrillation. Quinidine is subsequently introduced if reversion to normal sinus rhythm is desired. In the presence of a recent myocardial infarct, or mitral stenosis, or in any other heart disorder in which embolism is likely to occur, anticoagulant treatment is indicated. It is imperative that good laboratory control be available when anticoagulants are used. There is no obvious contraindication to the use of quinidine simultaneously with digitalization or following it.[5] However, quinidine should never be employed in the presence of conduction defects or other evidence of digitalis intoxication. If there is no severe underlying heart disease and no factor which tends to perpetuate auricular fibrillation, such as hyperthyroidism or carditis, quinidine alone will usually restore normal sinus rhythm.

Quinidine sulfate, in doses of 0.4 Gm. given every two or three hours, will abolish most attacks of paroxysmal auricular fibrillation. If ineffectual after several doses, the dosage should be increased to 0.6 Gm. or higher. The

drug should be continued until conversion of the arrhythmia has occurred or symptoms of intoxication appear. Among these are tinnitus, diminished hearing, vomiting, diarrhea or allergic manifestations. It is advisable to give no more than five successive doses in a single 24 hour period. If the patient is vomiting, or if any other condition precludes the oral administration of quinidine sulfate, quinidine may be administered intramuscularly with an initial dose of 0.6 Gm. It is wise to take repeated electrocardiograms during parenteral quinidine administration and to be alert for the development of intraventricular or auriculoventricular conduction defects or other evidences of toxicity. Procaine amide (Pronestyl) may be effective in the conversion of this arrhythmia. The use and dosage of this drug will be discussed below under the treatment of ventricular tachycardia.

Quinacrine (atabrine) has recently been used in the treatment of paroxysmal auricular fibrillation.[6] It is reported to be as effective as quinidine in this arrhythmia and apparently has succeeded in the conversion of auricular fibrillation in cases where quinidine has failed. This would suggest that it may be of use for those patients who do not respond to or who may be sensitive to quinidine. Further clinical evaluation of this drug in the treatment of auricular fibrillation is necessary.

Paroxysmal Auricular Flutter

Most patients with this rhythm have some type of structural heart disease although, as in paroxysmal auricular fibrillation, it is sometimes encountered in patients with normal hearts. Acute infections and hyperthyroidism are known to cause this arrhythmia.

In most cases of auricular flutter the patient is aware of the disturbance but is commonly in no great distress. However, heart failure may be present or may ensue, especially where the ventricular rate is rapid. While auricular flutter will occasionally respond to quinidine or to procaine amide, it is probably advisable to digitalize all patients with paroxysmal auricular flutter as soon as the arrhythmia is recognized. This is indicated particularly when there is a rapid ventricular rate, or when congestive failure is present or impending.

If flutter should occur in a patient with a recent myocardial infarct, and digitalis or quinidine is to be used, it is not necessary to employ anticoagulant therapy, as when auricular fibrillation occurs following infarction, since embolism rarely if ever takes place during flutter.[7]

When acute heart failure is associated with flutter, ouabain, lanatoside C, or Digoxin should be given intravenously, provided the patient has not received a digitalis preparation during the previous 14 days. If heart failure is not present or is of mild degree, digitalization may be accomplished orally over a period of a day or so, using the whole leaf of digitalis, or whatever glycoside the clinician prefers. Digitalis therapy usually results in one of the following eventualities: the flutter may be converted to fibrillation and remain as such; fibrillation may then be converted to normal sinus rhythm with quinidine, usually after digitalis has first been discontinued; fibrillation may revert to sinus rhythm spontaneously after withdrawal of digitalis without the necessity of using quinidine; or flutter may persist despite digitalization. In the latter instance, quinidine should be tried, as described under treatment of auricular tachycardia.

Ventricular Tachycardia

Ventricular tachycardia occurs, as a rule, in the presence of various structural changes in the heart, especially during the course of myocardial infarction. It is one of the most serious complications which may occur following infarction. Occasionally it is caused by digitalis intoxication, particularly in a patient with a seriously impaired myocardium. Uncommonly it occurs in a normal heart.

The presence of this arrhythmia should be suspected in any patient with heart disease who has a sudden change of heart rate to 160 to 200 or more beats per minute and which is basically regular in rhythm. It is well to remember that it can occur in complete heart block and that it may lead to bouts of ventricular fibrillation which, with ventricular tachycardia, may be a cause of Adams-Stokes seizures.

It is imperative that this rhythmic disturb-

ance be abolished as soon as possible because of the ever present possibility that ventricular tachycardia may become ventricular fibrillation with fatal outcome. Treatment consists of absolute rest, induced, if necessary, by morphine administered subcutaneously or, in emergency, intravenously. At present, quinidine still remains the drug of choice in terminating this arrhythmia. A dose of 0.6 Gm. should be given orally and repeated every two hours until the rhythm reverts to one of sinus origin or until there are evidences of toxicity. These may first be evident in electrocardiograms, which ideally should be taken before each successive dose. Electrocardiographic evidences of quinidine toxicity are conduction defects, chiefly with increase in QRS and the Q-T interval and lowering of the voltage. Recently several preparations (quinidine hydrochloride, quinidine dihydrochloride, quinidine lactate, quinidine gluconate, and quinidine sulfate) have become available which can be given *intramuscularly* without serious reactions. The recommended initial dose is 0.6 Gm. In desperate cases, quinidine may be used *intravenously* employing 0.6 Gm. diluted in 5 per cent glucose solution and given by the drip method. During quinidine administration, particularly when the drug is given parenterally, it is advisable to obtain serial electrocardiograms to follow the efficacy of treatment accurately and to watch for signs of toxicity. One authority[8] has recently reported the intravenous route of administration to have been successful in 20 out of 31 attacks. Despite this favorable result we should like to emphasize great caution in the intravenous administration of any form of quinidine because serious or fatal reactions may occur. It would be well if this route were used only when all other agents have failed and only if the patient is in a critical state.[9]

A new drug has recently made its appearance for use in the control of ventricular tachycardia. This is procaine amide hydrochloride (Pronestyl hydrochloride).[10] It appears to be sufficiently effective to offer promise. In a reported series, it failed in only two of 32 episodes of ventricular tachycardia.[11]

Preliminary observations of our own and others indicate that procaine amide is also effective in the treatment of supraventricular arrhythmias. These include paroxysmal auricular and nodal tachycardias, auricular fibrillation, and auricular flutter. Procaine amide may be used as a substitute for quinidine; it may be tried in cases where quinidine treatment has been unsuccessful, or where there is intolerance to the latter drug. Like quinidine, procaine amide appears to be least effective when the arrhythmia has been of long standing.

Procaine amide may be employed both orally and intravenously; the latter route has been observed to cause a marked though transient fall in blood pressure. Nausea and vomiting have been noted occasionally as side effects but only where large doses are given orally. Clinical experience to date indicates procaine amide may be less toxic and more effective than quinidine in ventricular tachycardia. Evidence suggests that it is less dangerous when given intravenously than quinidine given by the same route. The dosage recommended for the administration of procaine amide is necessarily provisional at this time because of the limited number of cases which have been studied. The following dosage schedules are suggested: For oral use the drug is supplied in capsules of 250 mg. The oral route is advised with an initial dose of 1.25 Gm. This dose is frequently effective. If there has been no response and no evidence of toxicity, a second dose of 0.75 Gm. may be given in one hour. Further doses of 0.5 to 1.0 Gm. may be given at two to four hour intervals thereafter as required to terminate the aberrant rhythm. Procaine amide is supplied for parenteral (intravenous) use, in ampules of 10 cc., each cc. equivalent to 100 mg. The intravenous route is preferable only in patients who are unable to take oral medication or in acute emergencies, as when shock or failure are impending. The maximum rate of intravenous administration should be 200 mg. per minute, stopping the treatment when the rhythm reverts to normal, if there is any untoward effect or toxicity such as a fall in blood pressure, or when a total of 1 Gm. of procaine amide has been given. No more than 1 Gm. of the drug should be administered as a single intravenous dose. As in the use of parenteral quinidine it is helpful to take electrocardio-

grams, preferably with a direct-writing instrument, during intravenous administration. Procaine amide appears to have a quinidine-like action upon the heart. The toxic effects seen on the electrocardiogram are very similar to those of quinidine. They include prolongation of QRS and the Q-T interval and decrease in voltage. Rarely, ventricular tachycardia and ventricular fibrillation have resulted from procaine amide apparently because of too rapid administration or intravenous dosage in excess of 1 Gm.

In the treatment of ventricular tachycardias this new drug may make unnecessary trial with less effective agents, including magnesium sulfate, potassium chloride or Paredrine hydrobromide.

Although digitalis and its glycosides may, in toxic doses, produce ventricular tachycardia, the number of instances in which this occurs is probably small. The use of digitalis in the presence of ventricular tachycardia following myocardial infarction has recently been reviewed.[12] Symptoms, which could have been interpreted as being due to digitalis intoxication in three patients with ventricular tachycardia and heart failure, disappeared in spite of the continued use of digitalis. The conclusions seem to indicate that digitalis may be used safely in the treatment of ventricular tachycardia when congestive heart failure is present. However, this requires further investigation before it can be completely accepted.

Complete Heart Block

This rhythmic disturbance may cause no symptoms. However, with the occurrence of an Adams-Stokes seizure, emergency treatment often becomes imperative. Dizziness and syncope, with or without convulsions, are the main symptoms of the syndrome.

Since the Adams-Stokes syndrome may be initiated by ventricular tachycardia or by ventricular fibrillation or may be caused by complete ventricular asystole, differential diagnosis must be decided by the electrocardiogram. The treatment is different depending upon which of the mechanisms is responsible. If the attack is due to ventricular tachycardia or fibrillation, quinidine or procaine amide appear to be the drugs of choice, used as outlined previously.

If an Adams-Stokes seizure is the result of asystole of the ventricles, epinephrine, 1 cc. (1:1000 dilution), is the drug to be used. It should be administered by injection into the heart. This may be followed by ephedrine sulfate, 25 mg. subcutaneously every four hours. If ventricular standstill continues, Paredrine hydrobromide[13] should be tried, also by injection into the heart. If cardiac standstill should occur while a patient is undergoing an operation, manual massage of the heart or direct electric stimulation of the ventricles of the exposed heart should be performed.[14]

If congestive heart failure occurs in the presence of complete heart block, digitalis should be administered. There is no contraindication to its use in this condition unless, of course, the arrhythmia is the result of digitalis intoxication.

Congestive Heart Failure

This condition is not infrequently an emergency in those instances where failure has appeared rapidly, or when a patient in congestive heart failure is in need of immediate surgical or obstetric care. Regardless of the type of heart disease, the basic principles of treatment are much the same. Management should be modified by the nature of the precipitating cause of the congestive heart failure. For example, if a myocardial infarct has induced heart failure it is considered advisable to use anticoagulant therapy, as well as such drugs as digitalis or one of its glycosides.

The greatest immediate benefit is accomplished by reducing the excessive burden carried by the impaired heart. This can be done by placing the patient at complete rest but not necessarily confined to bed. If there is considerable anxiety or pain, morphine should be administered subcutaneously or intravenously.

If there is no contraindication, particularly the use of digitalis within the previous two weeks, ouabain, Digoxin, or any rapidly acting digitalis preparation should be given intravenously, regardless of the heart rhythm. The initial dose of ouabain should be 0.5 mg., repeating 0.1 mg. every half to one hour or until therapeutic effect has been obtained, for a total of not more than 1 mg. Digoxin may be given with an initial dose of 0.5 mg., intravenously,

followed by 0.25 mg. every four hours until a favorable response or a maximum of 1.5 mg. have been given. When using lanatoside C intravenously the first dose is 0.8 mg. followed by 0.4 mg. every two hours if needed to obtain a therapeutic response. Total dosage should generally not exceed 2.4 mg.

Acute Left Ventricular Failure

This emergency occurs most commonly in patients with the hypertensive type of heart disease. Left ventricular failure may occur also during or after operation, particularly if saline infusions or transfusions have been administered rapidly or in large quantity to a patient with structural heart disease. The prominent symptom is paroxysmal dyspnea; cough is also common. This initial phase may progress to pulmonary edema; then there is often expectoration of pink, frothy, watery sputum which may be raised in mouthfuls.

Morphine sulfate, 15 mg., combined with atropine sulfate, 0.6 mg., should immediately be administered hypodermically. If the urgency of the situation demands, morphine may be given intravenously. Nitroglycerin, when given early, seems to benefit some patients. The patient should be placed in Fowler's position or allowed to sit in a chair, where he will frequently be more comfortable than in bed. Oxygen therapy should be started as soon as possible. It should be administered by means of an oxygen mask metered for positive pressure (Meter Mask)[15] if available. With this method accurate control of pressure can be obtained by conducting the patient's expired air through water in a bottle calibrated in centimeters. It is advisable to begin with a pressure of 5 cm. of water which is gradually reduced to 1 cm. A concentration of 40 to 60 per cent oxygen with a volume flow of 8 to 10 liters a minute should be employed. Although masks are comfortable for some patients, they are objectionable to others. When discomfort prevents the administration of oxygen by mask, a change should be made to a tent, since this is an effective means of administrating 50 to 60 per cent oxygen. In order to obtain this concentration a maintenance flow of 10 to 12 liters per minute is necessary. Although a nasal catheter in the nasopharnyx is as a rule more comfortable for long continued use, it is not as effective as the mask since the highest concentration possible by this method is only 40 per cent. A flow of 7 liters of oxygen a minute must be employed in order to maintain this concentration. Unfortunately, mouth breathing, which is quite prevalent, lowers the oxygen percentage in the air inhaled.

If the patient has not had any digitalis in the previous two weeks, ouabain, lanatoside C, Digoxin, or any other rapidly acting preparation, should be given intravenously. The dosage to be used has been described. However, if the patient is to undergo an emergency procedure such as an operation or an obstetric delivery, it is advisable to supplement and maintain the effects produced by a rapidly dissipated parenteral glycoside with the simultaneous administration of an oral digitalis preparation.[16] One advantage of this procedure is that rapid and complete digitalization is accomplished within 6 to 12 hours. The other is that it dispenses with the necessity of administering a digitalis preparation at repeated intervals during the first 24 hours. By this method, maintenance dosage may be started 24, or if necessary, 48 hours after initial digitalization which is performed as follows: a single dose of one of the rapidly acting glycosides is given parenterally. Simultaneously, a dose of one of the more slowly acting digitalis preparations is given orally, in a dosage depending on the estimated weight of the patient. Experience with this procedure has been most satisfactory, employing ouabain in a dose of 0.5 Gm., intravenously, and the whole leaf tablet of digitalis (New York Heart Association Preparation, U.S.P. XIII) orally, in amounts ranging from 0.4 Gm. to 0.8 Gm., depending on body weight: 0.4 Gm. of digitalis leaf for weights to 125 pounds, 0.6 Gm. for weights of 125 to 175 pounds, and 0.8 Gm. for patients who weigh 175 pounds or more.

If for any reason a digitalis preparation cannot be used, aminophylline, 0.24 Gm., should be administered intravenously. It should be given slowly to avoid such reactions as headache, vertigo, palpitation, and possibly precordial pain or substernal oppression. It is best not to give this medication intramuscularly

because of the intense local irritation which it usually causes. Suppositories of aminophylline are sometimes helpful as a substitute for, or as a supplement to, intravenous administration. The suppositories are supplied in 0.24 and 0.48 Gm. sizes. They are particularly useful in that they can be used by the patient at the onset of a bout of paroxysmal dyspnea and sometimes lessen the severity of the attack.

"Bloodless phlebotomy" may be an effective adjunct to treatment if pulmonary edema is accompanied by venous engorgement. The purpose of this procedure is to utilize the peripheral venous system as a reservoir, decrease the circulating blood volume, and thereby diminish the venous return to the heart. It is accomplished by applying tourniquets, preferably blood pressure cuffs, to all four extremities. Three of the cuffs are inflated at a time to a pressure slightly higher than the level of the patient's diastolic pressure. Release of each cuff is done in rotation every fifteen minutes to permit re-establishment of adequate blood flow. If this, and the measures outlined above, have not been successful in relieving the acute failure, phlebotomy, with the rapid withdrawal of at least 500 cc. of blood, should be performed.

Since the maintenance of an edema-free state is important, particularly in paroxysmal dyspnea or pulmonary edema, a mercurial diuretic should be administered intramuscularly or subcutaneously shortly after the measures described above have been initiated. A new mercurial diuretic, Thiomerin, which may be administered subcutaneously, intramuscularly, or intravenously, has been employed with excellent results.[17, 18] Based on ease of administration, degree of diuresis, and local tolerance, it is now considered by many to be the diuretic of choice.

Shock in Myocardial Infarction

Shock may be a complication of myocardial infarction. Its development is of very serious prognostic significance, as it is one of the main causes of death in the initial period following infarction.

The fall in blood pressure, which is often noted as part of a coronary attack, does not of itself constitute shock, even when systolic pressures of 90 mm. Hg or lower are present. Congestive failure, which not uncommonly occurs as a consequence of myocardial infarction, and which may be present concomitantly, should also not be confused with this condition.

Shock is identified by the following characteristic findings: The patient may be restless and apprehensive but he is more often in a semicomatose or comatose state. There is extreme pallor or cyanosis and the skin is cold and moist. The peripheral pulses are weak, thready or undetectable. The systolic pressure is usually 90 mm. Hg, or lower, and the pulse pressure is small; in patients who have previously manifested hypertension, the systolic pressure may be considerably higher than this figure.

Therapy should be based upon an understanding of the pathologic physiology which is responsible for the condition. Unfortunately, fundamental data concerning these mechanisms are inadequate and incomplete. There remains considerable controversy as to whether the primary mechanisms are cardiogenic or due to factors related to the vascular system. Because this process is not completely understood, plans of management of shock following myocardial infarction vary from the practice of "judicious neglect" to the use of a conglomeration of drugs and procedures based upon varied theoretic concepts.

The following are the most accepted measures in treatment: Elevation of the foot of the bed is of some value but is contraindicated if congestive failure is also present. High concentrations of oxygen administered by mask or tent should always be instituted as soon as possible. Artificial heating units should not be employed since burns may be easily produced in the presence of poor peripheral circulation and diminished sensory perception. Also, excessive sweating, due to external heat, may cause an additional loss of needed body fluids. The patient should, however, be covered with blankets sufficient to keep him comfortably warm. Bandaging the lower extremities from ankle to midthigh is thought by some to be of value. The use of the vasoconstrictor drugs is apparently increasing, although the question of their indication is controversial. These medications include Neosynephrine, ephedrine,

Paredrine, and possibly norepinephrine. Paredrine is given in dosage of 10 to 20 mg. intramuscularly, or 5 to 10 mg. intravenously. The dosage of Neosynephrine is 5 mg. subcutaneously, or a maximum of 0.3 mg. may be given intravenously in dilute solution.

Morphine is indicated only if the patient is extremely restless, anxious, or in considerable pain. Otherwise it is contraindicated because the opiates depress pulmonary as well as tissue respiration and thereby tend to increase the degree of anoxia which is frequently present.

It is known that if shock following myocardial infarction is treated with these measures alone, the mortality is still about 80 per cent. In view of this high mortality, more dynamic forms of therapy, if proved effective and not potentially too dangerous, would seem to be indicated. Until there is adequate understanding of the causative factors in this form of shock, we can only be guided in its treatment by experimental and clinical results following trial with various therapeutic measures.

Investigative studies on dogs appear to indicate that the early transfusion treatment of shock following coronary occlusion will improve failing myocardial contraction of the ischemic area and thereby probably increase cardiac output.[19] This work seems to justify the use of emergency measures directed at rapidly relieving acute shock following myocardial infarction, principally with the use of transfusions of blood or plasma and perhaps also with vasoconstrictor drugs.[19] Since hemoconcentration is frequently present, plasma transfusions may be preferable.

In recent years, some clinicians have advised the use of transfusions in this form of shock.[9] Reported clinical experiences with intravenous transfusion in the treatment of shock following myocardial infarction[20, 21] indicate that, while intravenous transfusions are not as yet of proved value, they have usually resulted in at least transient improvement. Where the treatment has failed it has appeared that larger, more frequent, or more rapidly administered transfusions might have reversed the shock picture or prevented recurrence. It has also been noted rather surprisingly that heart failure has rarely been produced by transfusions employed in this condition. Occasionally, indeed, where some degree of failure has been present at the time the transfusion was started, the signs have cleared following treatment. On the basis of experience thus far, it appears that the use of transfusions following myocardial infarction is only definitely contraindicated when a high venous pressure, or marked pulmonary edema, is present.

Experimental studies[22] and preliminary clinical trials[23, 24] indicate that intra-arterial transfusions may be superior to intravenous transfusions in the treatment of this type of shock. Theoretic advantages of the intra-arterial, as compared with the intravenous route, are that intra-arterial transfusions effect a more prompt increase in blood pressure and probably of circulating blood volume. Consequently, there should be less danger of immediate overloading of the heart than with the use of larger intravenous transfusions. Experimental work on dogs in shock[22] has shown rapid retrograde perfusion of renal, coronary and cerebral arteries following arterial transfusion. In view of these considerations the use of intra-arterial transfusions of blood or plasma in the treatment of "coronary shock" warrants further investigation and evaluation.

Shock Following Pulmonary Embolism

Another form of shock which may be considered a cardiac emergency is that which frequently follows pulmonary embolism. Pulmonary emboli usually come from thrombi in the deep veins of the lower extremities or from the veins of the pelvis in surgical and obstetric patients. Symptoms are variable but in typical cases the patient suddenly becomes acutely dyspneic and cyanotic, is restless and anxious, complains of severe substernal oppression, and often there is rapid progress to shock and death. Differential diagnosis between pulmonary embolism and acute myocardial infarction may be difficult. History, x-ray, and especially the electrocardiogram are helpful in the diagnosis. Unfortunately, myocardial infarction is known to occur secondary to pulmonary embolism, in which circumstance evidences of both conditions will coexist. Prognosis of pulmonary embolism depends chiefly upon the size of the

embolus, the severity of secondary reflex effects, and the promptness with which treatment directed at the relief of these factors is instituted.

In the treatment of this condition, oxygen should be given as soon as available. Morphine, combined with atropine, is administered if the patient is acutely dyspneic and is suffering from pain or anxiety. Vasodilator drugs are probably of considerable value in the presence of reflex vasospasm, but they should not be given if shock has developed. These medications include papaverine, 0.06 Gm., aminophylline, 0.48 Gm., and atropine, 0.6 mg., which are given by the intravenous route.

Anticoagulants have become one of the most important factors in reducing mortality and morbidity following pulmonary embolism. They are given to prevent propagation of thrombus in the pulmonary vessels and in an effort to control further embolization from the primary site. Heparin, because of its rapid action, should be given as early as possible. It is best administered intravenously in doses of 75 to 100 mg. which are repeated at six hour intervals until dicumarol or one of the more slowly acting anticoagulants, given simultaneously, has become fully effective. Proper laboratory control is, of course, essential. If further embolization occurs despite adequate anticoagulant therapy, bilateral femoral vein ligation and even ligation of the inferior vena cava may be indicated.

It should be kept in mind that pulmonary embolism can usually be prevented by the use of anticoagulants and the other prophylactic measures which should be employed in conditions where thromboembolic phenomena are apt to occur.

Cardiac Tamponade

Although this condition is not common it constitutes a serious emergency, which, if not treated promptly and properly, will invariably lead to death. The diagnosis of tamponade is missed with sufficient frequency to warrant a brief discussion to aid in its recognition.

Acute tamponade of the heart may occur following injury to the heart, to the pericardium, or to the great vessels. It results commonly from stab or gunshot wounds, but it may also complicate infections of the pericardium if there is considerable effusion. This is especially liable to occur in acute suppurative pericarditis. Rare, and invariably fatal, causes of tamponade are rupture of the heart following myocardial infarction, and retrograde progression of a so-called dissecting aneurysm of the aorta.

Patients with wounds and tamponade of the heart may be restless or in profound shock when first seen. The pulse is usually weak, thready, or imperceptible. Classically it is paradoxical in type. The blood pressure is commonly very low or unobtainable. The veins of the neck are distended. Heart sounds are generally distant or inaudible.

In the treatment of this condition aspiration of the pericardial space is usually indicated as an emergency measure to relieve tamponade. Early aspiration is also necessary because this blood clots rather rapidly and can be easily removed only soon after bleeding occurs. Fortunately, in many instances the bleeding does not recur and subsequent operation is not necessary.[25] However, if aspiration is not successful, or if signs of tamponade recur, open operation with suturing of the incised myocardium is indicated.

An aid in therapy which may help to prevent circulatory failure in acute pericardial tamponade is the rapid administration of intravenous infusions of saline, or of other intravenous solutions.[26, 27] The increase in venous pressure produced by this means will frequently overcome the resistance to the return of the blood to the right heart caused by tamponade. This increase may be sufficient to permit improvement in cardiac filling, and therefore of cardiac output. The result of this treatment is largely dependent upon whether the pericardial sac is able to stretch further. Intravenous infusion alone may aid in maintaining the circulation of the patient with tamponade. At least this appears to be a supportive measure which may be a valuable adjunct to aspiration or surgery.

A useful routine has been suggested[27] in the treatment of cardiac tamponade following stab wounds of the heart. The patient is given an infusion of saline solution and fluoroscoped immediately. If there are clinical and x-ray signs of tamponade, aspiration is performed

immediately. The patient then receives a transfusion. If aspiration is unsuccessful or if the signs of pericardial tamponade recur after a successful aspiration, the heart is sutured.

Cardiac tamponade may also result from empyema secondary to acute suppurative pericarditis, or from large effusions such as are found in tuberculous pericarditis. Tamponade due to these causes produces circulatory failure of the same type as that observed in patients with stab wounds of the heart. It is treated by aspiration or by surgery with open drainage if aspiration is inadequate. Penicillin or other antibiotics may be of value when instilled directly into the pericardial sac in suppurative pericarditis following initial aspiration or surgical drainage. This is usually supplemented by systemic antibiotic therapy.

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ABSTRACTS

Editor: SAMUEL BELLET, M.D.

Abstracters

BACTERIAL ENDOCARDITIS

Kane, L. W., and Finn, J. J., Jr.: The Treatment of Subacute Bacterial Endocarditis with Aureomycin and Chloromycetin. New England J. Med. **244:** 623 (April 26), 1951.

Eleven patients with subacute bacterial endocarditis were studied. Eight were treated with Aureomycin. In only two cases in whom Aureomycin was used initially were cures obtained. In no instance was Aureomycin successful when penicillin previously had failed. In two cases, however, penicillin was effective after Aureomycin had proved unsuccessful. Aureomycin was no more effective against *Streptococcus faecalis* than penicillin, although the organism was highly sensitive to Aureomycin in vitro. All patients treated with Aureomycin exhibited gastrointestinal symptoms. Of the five cases treated with Chloromycetin, only one could be classified as a cure. In two cases large doses of penicillin resulted in a cure where Chloromycetin had been ineffective. The authors conclude that penicillin is the antibiotic of choice in the treatment of subacute bacterial endocarditis due to *Str. viridans* and *Str. faecalis*. Aureomycin or Chloromycetin should be tried if in vitro studies are favorable and if the patient has not responded to large doses of penicillin or to a combination of penicillin and streptomycin.

SAGALL

BLOOD COAGULATION

Barker, **N. W., Estes, J. E., and Mann, F. D.: Clinical Experiences with the Anticoagulant, Ethyl Biscoumacetate (N.N.R.).** Proc. Staff Meet., Mayo Clin. **26:** 162 (April), 1951.

The authors' experiences confirm previous reports that ethyl biscoumacetate (Tromexan) is a satisfactory anticoagulant for clinical use. Ethyl biscoumacetate acts somewhat more rapidly than dicumarol after the first dose has been administered, and its effect disappears somewhat more rapidly when administration is stopped. Menadione sodium bisulfite appears to have accelerated the return of the prothrombin time to normal in a limited number of cases in which ethyl biscoumacetate has been used. Their experience has shown somewhat more difficulty in maintaining the hypoprothrombinemia within the therapeutic range, particularly during the first 7 to 10 days of treatment, when ethyl biscoumacetate was used than when dicumarol was used, because of the tendency to more marked fluctuations in the prothrombin time from day to day. As has been noted in experiences with dicumarol, the administration of fixed doses of ethyl biscoumacetate is followed in different patients by variable responses which cannot be predicted in advance, and frequent determinations of the one stage prothrombin time are essential as a guide to effective and safe administration of this anticoagulant.

SIMON

CONGENITAL ANOMALIES

Calazel, P., Gerard, R., Daley, R., Draper, A., Foster, J., and Bing, R. J.: Physiological Studies in Congenital Heart Disease. XI. A Comparison of the Right and Left Auricular Capillary and Pulmonary Artery Pressures in Nine Patients with Auricular Septal Defects. Bull. Johns Hopkins. Hosp. **88:** 20 (Jan.), 1951.

In nine patients with auricular septal defects,

pulmonary capillary, pulmonary venous, left auricular, right auricular, and pulmonary artery pressures were recorded. There was no resemblance between the tracings of the pulmonary capillary pressure and the pulmonary artery pressure or the left auricular pressure. The tracings from the left auricle differed from those from the right auricle in that there was a sharper presystolic upstroke, a steeper fall due to the descent of the base, and a more rapid second rise during auricular diastole. The mean pulmonary capillary pressure ranged from 6 to 19 mm. Hg with an average of 12 mm. Where the catheter did not obstruct the pulmonary vein, the mean pressures ranged from 8.5 to 13 mm. Hg, with an average of 11.5 mm. Hg. If the pulmonary vein was obstructed by the catheter tip, there was a rise in the mean venous pressure. The mean left auricular pressure ranged from 6 to 12 mm. Hg with an average of 9.5 mm. and the mean pressure in the right auricle ranged from 4 to 10 mm. Hg with a mean of 9.4 mm. There were three patients in whom the mean right auricular pressure exceeded the left auricular pressure. In these patients, pulmonic stenosis or tricuspid atresia was present. Where the left auricular pressure exceeded 10 mm. Hg, the pulmonary capillary–left auricular pressure gradient increased. Therefore, the authors believe that the pulmonary-capillay pressure does not represent left auricular pressure if the latter is above 10 mm. Hg. In patients with right to left shunt, the pressure in the right auricle exceeded that in the left during the whole cardiac cycle. In patients with left to right shunts there was a short period at the onset of auricular filling where the right auricular pressure exceeded that in the left. It is felt that this reversal in pressure gradient may be sufficient to result in a small right to left shunt through the defect. There was no relationship between the pulmonary capillary and pulmonary artery pressures.

MARGOLIES

Castellanos, A., and Garcia, O.: Classification of the Anomalies of the Pulmonary Artery and its Branches. Arch. d. mal. du coeur **44:** 193 (March), 1951.

Based on angiocardiographic studies, which are illustrated by numerous instructive diagrams, the authors present a classification of congenital anomalies of the lesser circulation. If anomalies of the pulmonary veins are excluded, four main groups can be distinguished: anomalies of the infundibulum, of the valvular orifice, of the main trunk and of the branches of the pulmonic artery.

The pulmonary conus (infundibulum) may be dilated, atresic or stenosed in its middle or lower portions. Anomalies of the valvular part of the pulmonary artery consist in abnormal origin of the vessel (from the left ventricle or overriding the septum), in anomalies of its diameter (dilatation, stenosis, or lack of perforation) or in absent, supernumerary or fenestrated valves. The main trunk of the pulmonic artery may have an abnormal caliber (hypoplasia to complete atresia or dilatation to aneurysmic deformity). It may further show an abnormal position in relation to the aorta or abnormal communication with the aorta (persistent ductus arteriosus, aortopulmonary aneurysm) and it may be completely absent (truncus arteriosus communis). The main branches of the pulmonary artery may be abnormal in number (agenesis of one or both branches), in size, in origin (directly from the aorta), or may show abnormal communications (arteriovenous aneurysms).

A great number of these anomalies can be diagnosed by the help of classic dextroangiocardiography, with the patient in a suitable position. Patency of the ductus arteriosus or a direct aortopulmonic communication can be visualized readily by retrograde aortography.

PICK

Leininger, C. R., Gibson, S., and Potts, W. J.: Congenital Pulmonary Stenosis. Am. J. Dis. Child. **61:** 465 (April), 1951.

The authors describe their postoperative observations on 214 children with congenital pulmonary stenosis. The preoperative diagnosis in 199 cases was tetralogy of Fallot, and in 15 cases, tricuspid atresia. In 177 cases, an aortic-pulmonary anastomosis (Potts-Smith) was done, in 21 cases, a Blalock operation, and in one case, a localized stenosis of the left pulmonary artery was resected. Fifteen children had exploratory thoracotomies, with no anastomosis being performed. Of this group, seven died shortly after surgery. Of the 199 children who had the anastomoses, 18 died in the immediate postoperative period, and one lost his life in an automobile accident. One hundred forty-five of the remaining 180 patients have been observed for postoperative periods ranging from 6 to 42 months. During the period of observation, eight of these children (5.5 per cent) have died of varied causes.

Paroxysmal dyspnea which occurred in 66 children before surgery was not observed postoperatively. Squatting also disappeared after the successful anastomosis. The red blood count and the hemaglobin averaged 6,930,000 per cu. mm. and 18.3 Gm. per 100 cc., respectively, prior to surgery, and 5,350,000 per cu. mm. and 14.4 Gm. per 100 cc. after operation. There was a marked and immediate decrease in the cyanosis following surgery. By the end of the first year, the changes in the clubbing of the fingers and toes were usually complete, but a suggestion of clubbing still persisted. There was usually an increase in the exercise tolerance which in some cases was dramatic. There has been cardiac enlargement to some degree after surgery, and should be expected if the anastomosis remains patent.

Significant and consistent electrocardiographic changes observed two to three years after surgery,

consisted of a decrease in the amplitude and the peaking of the P waves, and a disappearance of the evidence of right heart strain. The authors do not believe that this type of surgery removes the strain on the right ventricle, but believe that these changes occur because of better oxygen saturation in the coronary circulation, and the beginning of left heart preponderance. They further state that proper postoperative evaluation of these patients will require another decade or more. The immediate relief of symptoms with a change from a life of invalidism to one of relative normalcy justifies the procedure.

MARGOLIES

Goetz, R. H.: A New Angiocardiographic Sign of Patent Ductus Arteriosus. Brit. Heart J. **13:** 242, (April), 1951.

The author describes a sign he believes is pathognomonic of patent ductus arteriosis. This is characterized by a defect in the outline of the main pulmonary artery best seen in the left anterior oblique position two to three seconds after injection of a contrast medium. The defect is due to blood free of contrast medium flowing from the aorta through the ductus to the pulmonary artery.

SOLOFF

CONGESTIVE HEART FAILURE

McChesney, E. W., Dock, W., and Tainter, M. L.: Ion Exchange Resins in Edema. Medicine **30:** 183 (May), 1951.

The carboxylic and sulfonic types of ion exchange resins are described, and their important similarities and differences noted. These cation exchangers react according to known physical laws, possessing about equal affinity for ammonium and sodium, somewhat greater affinity for potassium, and still more for bivalent cations. However, the actual amounts of the various elements they pick up are determined not only by these affinities but also by the ionic concentrations in the intestinal tract. In the exchange process, ammonium or hydrogen ions are given up for sodium and potassium. Both reactions have an acidifying effect, since ammonium is converted in the liver to urea. For each 100 mEq. of cations taken up, 100 mEq. of ammonium or hydrogen are released, the equivalent of ingestion of 5.4 Gm. ammonium chloride or 100 cc. normal hydrochloric acid.

A survey of the experimental observations on animals shows the following results of resin ingestion: (a) sodium and potassium absorption from the gastrointestinal tract are reduced, and their fecal excretion increased; (b) the magnitude of these changes depends on the intake of cations and of resin; (c) the ratio of sodium to potassium picked up by the resin is equal to, or greater than, that in the diet; (d) significant changes in retention of sodium and potassium are seen in normal animals only when the diet is practically free of these ions, when low muscle concentrations of sodium and potassium develop before low blood levels; (e) calcium absorption is diminished by some resins and not by others; (f) uptake of cationic organic compounds including amino acids and vitamins has not been determined; (g) the effective capacity of resins in vivo is between 30 and 40 per cent of that in vitro, and the cation binding power is subdivided among sodium, potassium and calcium.

The authors have found from their experience and from review of current clinical investigations that similar results appear in edematous patients. Either carboxylic or sulfonic resins take up sodium, potassium, and possibly some calcium in the gastrointestinal tract, exchanging hydrogen or ammonium ions for them. This results in smaller absorption of these cations. The optimal dose of resin is about 40 to 100 Gm. a day. When administered at, or near, meal time the resins will divert from absorption about 1.2 mEq. sodium and 1 mEq. potassium per Gm. Thus, it is feasible to prevent the absorption of 1 to 2.5 Gm. sodium daily. This is often enough to result in a loss of edema fluid, even when diuretics have failed; or the resins may be used to supplement diuretics. Some degree of compensated acidosis appears with resin administration, but this is not considered harmful. The chief complication is potassium deficiency, which is most likely when dietary sodium is very low; a condition under which resins will pick up potassium in preference to sodium. This complication can be circumvented by the use of potassium-containing salt substitutes, by potassium citrate, by fruit juices, or by using a resin partly in the potassium cycle. Calcium deficiency has occurred infrequently, and may be related to long term resin therapy. Thiamine and magnesium deficiency have not presented any problem. Gritty, constipated stools have occurred after prolonged administration. The authors conclude that resin treatment warrants further use, and that it may well be used in hypertension to reinforce sodium restriction.

ENSELBERG

Donzelot, E., D'Allaines, F., Heim de Balsac, R., Dubost, Ch., Hamelberg, H.-F., Allary, M., Frileux, C., and Nogrette, P.: Results of Ligation of the Inferior Vena Cava in 50 Cases of Refractory Heart Failure. Arch. d. mal. du coeur **44:** 239 (March), 1951.

In a series of 50 cases with chronic congestive heart failure, including 38 cases of mitral valvulitis, two with aortic lesions, nine cases of hypertension and one case of myocardial infarction, ligation of the inferior vena cava had the following results: 33 cases (66 per cent) were definitely improved, seven cases showed transient or no amelioration and 10 cases (20 per cent) died following the operation. Clinical signs of improvement were seen frequently

immediately after surgery and 42 per cent of the patients could return to their profession. The main postoperative complication was the development of phlebothrombosis despite heparinization and early mobilization. The selection of patients suitable for the operation remains very difficult. It should be performed only after longer observation of the patient in a hospital and after careful evaluation of the effect of medical treatment.

PICK

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Vineberg, A., and Miller, G.: Internal Mammary Coronary Anastomosis in the Treatment of Coronary Artery Insufficiency. Canad. M. A. J. **64:** 204 (March), 1951.

Transplantation of the left internal mammary artery into the left ventricle was done in three patients as a treatment for coronary artery insufficiency. Although one patient died shortly after the operation, the other two appeared to have been improved at the time of the discharge.

There appeared to be no disturbance in cardiac function resulting from the implant procedure, and no evidence of hemorrhage or intramural hematoma. The implanted artery was found to be completely patent 62 hours after the implantation in the one fatality that occurred.

SCHWARTZ

Miller, R. D., and Edwards, J. E.: Cardiac Clinics CXXXVII. Abscess Formation in an Acute Myocardial Infarct: Report of Case. Proc. Staff Meet. Mayo Clin. **26:** 178 (May), 1951.

A case of acute myocardial infarction which became complicated by suppurative infection of the infarct is reported. The infecting organism was *Escherichia coli*. Acute pyelonephritis was present and was considered to be an accompaniment of an assumed septicemia.

Three other cases of abscess formation in an acute myocardial infarct reported in the literature are reviewed. In each of the latter the source of the septicemia was a pyogenic pneumonia. In one of these cases the abscess formation within the myocardial infarct was further complicated by rupture of the heart.

SIMON

Price, R. K.: First Effort Angina. Second Wind in Angina Pectoris. Brit. Heart J. **13:** 197, 1951.

The author reports 20 individuals who developed angina pectoris at the beginning of physical effort but were able with or without a slight pause to continue the physical effort without pain. This phenomenon is regarded as similar to the "second wind" in respect to dyspnea. He believes that this phenomenon occurs in one out of five individuals with angina. The prognosis is no different from ordinary angina. It can be prevented by nitroglycerin. It may be due to the inability of the coronary arterioles to dilate soon enough on first effort.

SOLOFF

Mounsey, P.: Prodromal Symptoms in Myocardial Infarction. Brit. Heart J. **13:** 215, 1951.

Forty of 139 instances of myocardial infarction had prodromal symptoms for three days to 12 weeks with an average of three and one-half weeks. The individual attacks lasted from five minutes to six hours, and occurred both at rest and after effort. A crescendo quality of the pain was obtained in 29. The electrocardiograms of four showed evidence of myocardial ischemia at rest, two showed ischemia on effort, four showed no ischemia at rest and were not subjected to effort. The mortality of those with prodromal symptoms was 15 per cent compared to 50 per cent of those without prodromal symptoms.

The prodromal symptoms are attributed to gradually decreasing lumen of a coronary artery with consequent increasing myocardial ischemia.

SOLOFF

ELECTROCARDIOGRAPHY

Pordy, L., Kolker, J., and Levy, H.: Paroxysmal Ventricular Tachycardia of Prolonged Duration. Am. J. Med. **10:** 254 (Feb.), 1951.

The treatment and clinical findings in an unusual, well studied case of prolonged ventricular tachycardia are reported in detail. Following an acute anterior wall myocardial infarction the patient developed recurrent attacks of paroxysmal ventricular tachycardia. The most prolonged of these lasted 57 days and displayed a retrograde Wenckebach effect electrocardiographically. Among the drugs used without great success were quinidine, intravenous quinine and procaine hydrochloride, magnesium sulfate, diethylaminoethanol hydrochloride, strophanthidin acetate, Mecholyl hydrochloride, propylthiouracil, and digitalis. On the fifty-sixth day of the continuous ventricular tachycardia, 0.4 Gm. of atabrine dihydrochloride were injected intramuscularly. The following day the patient experienced a severe bout of vomiting after which sinus rhythm returned. Subsequently additional bouts of ventricular tachycardia occurred and the patient committed suicide. The authors recommend the trial of atabrine in refractory cases of paroxysmal ventricular tachycardia, especially in those showing intolerance or idiosyncracy to quinidine.

HARRIS

Michaelides, G., and Frixos, C.: Coronary Sinus Rhythm and Extrasystoles. Arch. d. mal. du coeur **44:** 231 (March), 1951.

Among 10,000 electrocardiograms, the authors found five instances of coronary sinus rhythm and a single case of extrasystole originating in the same region. According to the authors, a sharp distine-

tion should be made between coronary nodal rhythm and coronary sinus rythm. In the electrocardiogram, the latter is characterized by inverted P waves in leads II and III, and a normal or only slightly shortened P-R interval, while in the former the P wave is upright in leads I to III and P-R distinctly shortened. In coronary nodal rhythm, the impulse takes its origin in the "auricular sinus" and is transmitted from above toward the base. This anomaly of rhythm is seen rather frequently and has no clinical significance. Coronary sinus rhythm, on the other hand, originates in the coronary sinus and the spread of the impulse in the auricle is reversed. It is seen only very rarely and in the presence of organic heart disease.

PICK

Hein, G. E., and Sanazaro, P. J.: Intermittent Bundle Branch Block of Long Duration. Arch. Int. Med. **87**: 694 (May), 1951.

A case of long-standing intermittent bundle branch block is described, in which direct or indirect vagal stimulation at all times abolished the block, when present. A review is presented of the clinical and experimental work relating to the presence of vagal action on intraventricular conduction. Most data indicate that such vagal action, when demonstrable, is inhibitory in nature. Possible rare exceptions may occur.

The existence of intermittent conduction defects for prolonged periods has led to the use of the term "functional," since the unfavorable prognosis attached to such lesions was not borne out. Such designation is not correct in view of the serious underlying heart disease which is usually present. Rather, it is probable that complete blockage of bundle branch conduction has not occurred. It might be presumed, therefore, that the intracardiac lesion is not so advanced as in permanent bundle branch block. It is this factor, rather than the conduction defect, that determines the prognosis.

BERNSTEIN

Rodstein, M., Gubner, R., Mills, J. P., Lovell, J., and Ungerleider, H. E.: A Mortality Study in Bundle Branch Block. Arch. Int. Med. **87**: 663 (May), 1951.

Bundle branch block is an infrequent lesion in the general population. Right bundle branch block is of much greater frequency than left bundle branch block, particularly in the younger age groups and is commonly associated with little or no demonstrable cardiovascular impairment. The presence of bundle branch block per se does not imply a high mortality in the absence of other cardiac abnormalities; hence the prognosis where block is found will depend on the underlying cardiac disease. The difference between the mortality in right and that in left bundle branch block is relatively slight.

BERNSTEIN

Shillingford, J., and Brigden, W.: The Vectorcardiogram in 100 Healthy Subjects Using a New Drawing Instrument: Brit. Heart J. **13**: 233, 1951.

The authors describe and present photographs of an integrating apparatus that scans a pair of scalar (conventional) electrocardiographic leads and which moves mirrors that cause a deflection of a light beam that is an integration of the two movements.

They describe the frontal, sagittal and horizontal vectorcardiograms obtained by this method in 100 normal adults aged 16 to 70 years. These patterns are similar to those obtained by elaborate electronic methods.

The vectorcardiograms are smooth except in the older age groups. The QRS loop varied from 0.06 to 0.1 second, with the apex reached in 0.03 to 0.05 second. The T loops tended to rotate in the same direction and their axis lay within a few degrees of the QRS loop. The return loop in some cases extended above the origin of the loop and the ratio of the height to the depth never exceeded 1:4.

SOLOFF

Alimurung, M. M., and Smith, R. M.: Electrocardiographic Studies during Operation for Coarctation of the Aorta. Brit. Heart J. **13**: 203, (April), 1951.

No serious electrocardiographic abnormalities were noted during operation on 10 individuals for resection of coarctation of the aorta. Those changes seen tended to occur at the time of clamping of the aorta. The changes are tachycardia in all, prolongation of the P-R interval in two and lowering and/or notching of the QRS without or with S-T segment depressions. After release of the aortic clamps, the tracings tended to revert to their preoperative appearance. The changes may be due to vagal stimulation and myocardial hypoxia.

SOLOFF

HYPERTENSION

Davis, L., and Tanturi, C. A.: Liver as a Factor in Experimental Renal Hypertension. Arch. Surg. **62**: 325 (March), 1951.

Reduction of the blood flow to the liver decreases the systemic blood pressure of dogs with an experimental renal hypertension produced by the use of Goldblatt clamps on the renal arteries. Reduction of the blood flow in the portal vein is more effective in lowering the systemic blood pressure than total occlusion of the arterial blood supply to the liver. In order to produce this decrease in the systemic blood pressure in dogs with an experimental renal hypertension, reduction of the blood flow to the liver must be sufficient to produce a fatty infiltration of the liver cells whose nuclei are well preserved. This pathologic change in the liver may or may not be detected by the presently accepted tests for liver function. Portocaval shunts were performed on the animals with partial occlusion of the portal

vein and those with partial occlusion of both the portal vein and the hepatic artery. This procedure did not alter the sustained reduction of the systemic blood pressure but did improve the general condition of the animals. The reduction in systemic blood pressure observed in these experiments does not occur immediately after partial occlusion of the portal vein, which fact suggests an indirect, rather than a direct, participation in the mechanism controlling the systemic blood pressure. These results also point out that the liver plays a role in the humoral mechanism involved in experimental renal hypertension and lend support to the two current theories which have been proposed to explain the mechanism of experimental renal hypertension.

BERNSTEIN

Chris, S. M.: Sympathectomy for Hypertension. Brit. M. J. **4708:** (March 31), 1951.

Using rigid criteria for operability, the author performed a sympathectomy by a simple transpleural approach upon the lower thoracic chain and its branches on 35 patients with essential and malignant hypertension. Over an average period of 18 months a survey of this group revealed that only 25 per cent of the series maintained a significant fall in blood pressure. On the other hand, 66 per cent of them have been relieved of incapacitating symptoms and have returned to work. The most successful results occurred in women who developed hypertension after pregnancy complicated by toxemia or eclampsia. Older patients with complicating disease did poorly. The author concludes that for a limited group of hypertensives, sympathectomy is a valuable palliative procedure.

TANDOWSKY

Bevans, M., Davidson, J. D., and Kendall, F. E.: Regression of Lesions in Canine Arteriosclerosis. Arch. Path. **51:** 288 (March), 1951.

In view of the fact that the morphologic aspects of both human and canine arteriosclerosis closely parallel each other, the authors believe that both are influenced by the same factors. They therefore studied the regression in canine arteriosclerosis that is noted as soon as the causative dietary factors are removed. The canine lesion is easily produced by cholesterol-thiouracil feeding. Dogs maintained for four months on such a regimen with blood cholesterol levels ranging from 700 to 1860 mg. per cent were examined with particular reference to the degree and site of maximum deposit of atheroma. The usual advanced atherosclerosis of cerebral, coronary and iliac arteries was noted in most dogs with 1200 mg. per cent cholesterol blood level. The thyroid arteries were also strikingly involved. Dogs similarly treated, but allowed to live for two months and four months after cessation of the experimental feeding, showed an unexpected disappearance or subsidence of the vascular lesion. The plaques flattened, the borders became poorly marginated and microscopy showed in such areas only slightly thickened intima with little or no lipid. The blood cholesterol levels quickly recede to normal on stopping the special diet. The interesting feature was the definite regression and ultimate disappearance of the lesion of atherosclerosis on normalizing the diet.

GOULEY

Wilkins, R. W., Culbertson, J. W., and Ingelfinger, F. J.: The Effect of Splanchnic Sympathectomy in Hypertensive Patients upon Estimated Hepatic Blood Flow in the Upright as Contrasted with the Horizontal Position. J. Clin. Investigation **30:** 312 (March), 1951.

Before sympathectomy tilting into the upright position led to reductions in estimated hepatic blood flow with little change in pressure or increase in hepatic-portal resistance. After lumbodorsal splanchnicectomy, reductions of hepatic blood flow in hypertensive patients were associated with sizeable decreases in arterial pressure and with little change in average hepatic-portal resistance. The authors conclude that the splanchnic sympathetic system mediates the portal vasoconstrictor response to the upright position in hypertensive, and probably normal, subjects.

WAIFE

Griep, A. H., Barry, S. R., Hall, W. E., and Hoobler, S. W.: The Prognosis in Arterial Hypertension. Am. J. M. Sc. **221:** 239 (March), 1951.

A group of 117 hypertensive patients under the age of 53 years at the time of their initial studies were evaluated 8 to 10 years later either by letter to their physician or by re-examination. The patients selected were those who would have been considered candidates for splanchnicectomy, with blood pressures exceeding 160/110 and without primary renal disease, congestive failure, recent cerebrovascular accidents or severe renal impairment.

Of the original group, 46 per cent were alive at the end of the 10 year period; of those who died, 46 per cent died of hypertensive complications and 8 per cent died of other causes. The hypertensive deaths were almost equally divided between cerebrovascular accidents and cardiac causes; uremic deaths were uncommon. In this series it was not possible to predict the type of death to which the patient would succumb.

Important factors influencing prognosis in hypertension were: (1) hypertensive complications, such as left ventricular enlargement, electrocardiographic abnormalities, history of cerebrovascular disease, focal encephalopathy and persistent albuminuria; (2) sex (females outlived males 3:2); (3) the levels of diastolic blood pressure; (4) gradations of retinal vascular disease. The age of the patient and duration of hypertension were of little prog-

nostic value. The most important factor in prognosis was the presence of hypertensive complications (1) as 80 per cent of patients having such findings died, whereas only 20 per cent of those without evidence of vascular damage died in the 10 year interval. Of the survivors, 80 per cent are capable and useful individuals (35 per cent of the total group). Significant reductions in blood pressure occurred in four patients, two have normal pressures. Generally there was little change in the blood pressure of the survivors and the benign course of the disease in the absence of vascular complications is clearly shown.

SHUMAN

Adams, L. J., Notkin, M., and Pritchard, J. E.: Hypertension in Two Cases of Renal Artery Occlusion. Canad. M. A. J. **64:** 224 (March), 1951.

Two cases of severe hypertension showed gross obstruction at the orifices of the renal arteries at autopsy sufficient to reduce materially the renal blood flow. Atrophy and degeneration of the tubules in both cases were of a much greater degree than the glomerular and arteriolar lesions and were therefore attributed to the obstruction of the major renal arteries.

In the first case obstruction, due to nodules of hyperplastic intima, was bilateral and equal. In the second case, with a congenital anomaly, the arterial obstruction was predominantly unilateral and due to arteriosclerosis. Both cases lend additional support to the theory of a renal mechanism producing human hypertension.

SCHWARTZ

Davis, W. D., Jr., Segaloff, A., Jacobs, W. S., and Callahan, J. B.: The Effect of Desoxycorticosterone and Propylene Glycol in Experimental Hypertension. J. Lab. & Clin. Med. **37:** 499 (April), 1951.

This study was done to determine the effect of desoxycorticosterone and propylene glycol in both normal and hypertensive dogs.

The intravenous administration of propylene glycol was found to have an immediate pressor effect of about 15 to 30 mm. Hg and it lasted for about three minutes in both normal and hypertensive dogs. There was no difference in the blood pressure rise of the hypertensive and normal dogs.

The intravenous administration of 5 mg. of desoxycorticosterone acetate in 2 cc. of propylene glycol or 5 mg. of aqueous solution of desoxycorticosterone glucoside produced no additional pressor effect.

Desoxycorticosterone acetate given subcutaneously daily for a six-week period of time produced a gradual rise in blood pressure to a level of 25 to 50 mm. Hg above the control value following a gradual decrease to the normal level in about six weeks. In subsequent periods of observation with the same dogs and using the same dose of desoxycorticosterone acetate as had been previously used, or if the dose were doubled, approximately the same rise in blood pressure was produced as had been previously observed. There were no significant differences in the blood pressure responses of the normal and hypertensive animals. This same rise of blood pressure was found to occur in normal and hypertensive dogs with a high sodium intake. The rise in blood pressure could be abolished by rigid restriction of sodium in normal and hypertensive dogs.

MINTZ

Loofbourow, D. G., Callahan, D., and Palmer, R. S.: The Rice Diet in Ambulatory Patients with Essential Hypertension. A Two-Year Study of 105 Patients. New England J. Med. **244:** 577 (April 19), 1951.

Follow-up studies of a group of outpatients treated with the rice diet in 1947 and another group treated in 1948 are presented and evaluated. The authors conclude that the rice diet in most ambulatory patients produced no better results than more conservative medical therapy (weight loss, reassurance, mild sedation and psychotherapy). In certain patients severely ill with hypertension, however, the disease process apparently was dramatically reversed. The rice diet is unpleasant, monotonous, expensive and potentially dangerous and the justification of such a rigorous therapeutic regimen must be matched by the actual or impending rigors of the disease.

SAGALL

Bierman, H. R., and Partridge, J. W.: Untoward Reactions to Tests for Epinephrine-Secreting Tumors (Pheochromocytoma). New England J. Med. **244:** 582 (April 19), 1951.

Untoward severe but not fatal reactions were observed in four cases of a group of 56 separate tests performed on 21 patients suspected of having pheochromocytoma. Two patients showed reactions to 933 F (benzodioxane); the first developed a rise in blood pressure exceeding 300 mm. Hg and the second developed acute pulmonary edema. A third patient developed anuria for 14 hours after administration of Dibenamine. The fourth patient had a marked hypotensive response to tetraethylammonium bromide. These cases point out that pharmacologic tests for pheochromocytoma with adrenolytic substances are not without danger.

SAGALL

Dustan, H., Corcoran, A. C., Taylor, R. D., and Page, I. H.: Cortisone and ACTH in Essential Hypertension. Arch. Int. Med. **87:** 635 (May), 1951.

Cortisone or pituitary adrenocorticotropic hor-

mone (ACTH) in doses of 100 mg. daily had no definite or reproducible effects on arterial pressure in each of two pairs of patients with severe essential hypertensive vascular disease, although pressure decreased briefly in two after treatment was stopped. Of the specific renal functions (renal blood flow, glomerular filtration and tubular secretory capacity for paraaminohippurate, (Tm_{PAH}) renal blood flow was increased in two patients (one receiving cortisone and one receiving ACTH).

Urinary corticoids were not consistently increased in two patients given cortisone, but were increased in those receiving ACTH. ACTH treatment also depressed sweat sodium concentration in one patient, but, like cortisone, it had no effect on patients with low control levels of sweat sodium due to dietary restrictions. All four patients showed decreased serum cholesterol concentrations during treatment and a "rebound" to greater than control levels in the post-treatment period. Three of the four patients showed a decrease of maximum renal tubular reabsorptive capacity for glucose (Tm_g) during treatment. This persisted into the post-treatment period and was associated with glycosuria. Depression of this renal function seems to be an early and lasting result of hypercorticoidism.

BERNSTEIN

Cahill, G. F., and Monteith, J. C.: The Use of Dibenamine and Norepinephrine in the Operative Treatment of Pheochromocytoma. Report of Two Cases. New England J. Med. **244:** 657 (May 3), 1951.

Two cases of pheochromocytoma, one with a clinical picture of sustained malignant hypertension and the other with paroxysmal attacks, are presented. Because of its prolonged adrenolytic action, Dibenamine was administered to both patients during the immediate pre-operative period and apparently exerted its hypotensive effect during operative manipulation of the tumor. In both cases infusion of norepinephrine during the operation and the immediate postoperative period prevented a marked drop in blood pressure without producing the side effects occasionally encountered with epinephrine. After operation tests failed to reveal any excess pheochrome tissue.

SEGALL

PATHOLOGIC PHYSIOLOGY

Franke, F. R., Boatman, J. B., and George, R. S.: Effect of Adrenalectomy and DCA on the Radioisotope Intramuscular Clearance and Distribution in the Rat. Angiology **2:** 46 (Feb.), 1951.

Muscle clearance studies utilizing radioactive sodium (Na^{24}) and iodine (I^{131}) were performed on 60 control and adrenalectomized rats. The latter were maintained on desoxycorticosterone acetate (DCA) and saline. Clearance of radioactive sodium was increased in the adrenalectomized animals maintained on DCA alone. Because radiosodium clearances varied under experimental conditions, whereas radioiodine clearances remained essentially the same, the authors conclude that the two radioisotopes cannot be used interchangeably to quantitate peripheral circulation.

WESSLER

Baird, I. M., and Burne, J. C.: "Isolated" Myocarditis Associated with Unilateral Cortical Necrosis of the Kidney. Lancet **260:** 446 (Feb. 24), 1951.

Since Fiedler's original description of interstitial myocarditis, many other cases have been published with acute, subacute or chronic course. This disorder occurs mainly in young persons and sudden death is very common. The usual clinical picture is that of rapidly progressive heart failure in a previously healthy young person.

The case presented here is that of a 3 year old girl who died after a month's illness and in whom no etiologic agents could be ascertained to account for the diffuse myocarditis found at necropsy. A zone of unilateral cortical necrosis of the kidney was a feature of this case, and, despite the presence of antemortem thrombus in the left ventricle, the appearances of the renal lesion, by reason of its site and extent, were considered to be those of cortical necrosis and not infarction. Either vascular spasm or renal anoxia may have been the cause of the cortical necrosis.

BERNSTEIN

Lackey, R. W.: Glycogen Storage in the Heart in Experimental Renal Hypertension in the Rat. Science **113:** 184 (Feb. 16), 1951.

Chronically hypertensive rats showed no significant difference in liver glycogen or skeletal muscle glycogen when compared to control groups. However, the cardiac glycogen was significantly higher in the hypertensive rat. It had previously been shown that in conditions in which a ketonemia is produced there is a positive correlation between blood ketone levels and cardiac glycogen storage. In this experiment, no increase in blood ketones was found and, therefore, no evidence that the increased storage of glycogen by the hypertensive heart was related to a generalized disturbance in carbohydrate utilization.

WAIFE

Vicker, S. E.: Potassium Excretion in Rats. Science **113:** 187 (Feb. 16), 1951.

It is known that potassium is filtered through the glomeruli and reabsorbed partially by the tubule in normal man and animals. There is also some evidence that under certain circumstances potassium may be secreted by the tubules. During an experiment on sodium and potassium excretion in rats, a few instances were found in which the

potassium clearance was higher than that of inulin. This occurred in animals which, in spite of the administration of 5 per cent of their body weight of water had an abnormally low urine flow, probably as a result of accidental dehydration, and in rats in which the rate of urine flow is so high that a faulty measurement of urine volume was assumed.

From his calculations the author believes it likely that the enhanced potassium excretion was the result of a tubular secretion of that ion. Such secretion, however, did not seem to occur in newborn rats in which the depression of glomerular filtration seems to be the principle factor regulating renal excretion of potassium.

WAIFE

Gerling, F.: Effects of Intravenous and Intra-arterial Adrenaline, and of Adrenaline After Priscoline, in Hind Limb of Intact Rabbit. Am. J. Physiol. **164**: 400 (Feb.), 1951.

A new, simple, accurate method for continuous measurement of resistance is introduced. The proximal and distal ends of a femoral artery are cannulated. The two cannulas lead to a small chamber, separated from a recording mercury manometer by a slack rubber membrane. The pressure in the manometer is transmitted through the rubber membrane to the blood in the small chamber. Blood flows from the chamber via the distal cannula into the femoral artery. Short occlusions produce a downward projecting spike on the continuous blood pressure record: The length of the spikes, cross sectional area of the manometer tube, and duration of occlusion permit calculation of rate of flow at that point. Dividing the mean blood pressure by rate of flow gives the resistance. Using this method, intravenous epinephrine was shown to increase blood pressure and cause a vasoconstriction of progressive intensity. Maximum resistance is reached after pressure starts to fall. When epinephrine was injected intra-arterially there was no change in blood pressure. Increasing concentrations by this route first caused vasodilation, then dilation followed by constriction, and at highest values only constriction. Priscoline lowers blood pressure with vasodilation. When epinephrine follows Priscoline there is often a fall in pressure with vasodilation.

OPPENHEIMER

Batzner, K., and Bayer, H.: Arteriographic Observations Concerning the Velocity of Blood Flow in Lower Extremities with Impaired Circulation. Ztschr. f. Kreislaufforsch. **40**: 74 (Feb.), 1951.

The authors studied (a) the velocity of the blood flow in the affected leg and (b) the degree of reflectory response to stimulation of the anterior tibial muscle in 29 patients with disturbance of the circulation in the lower extremities, of various etiologies. The circulation time was determined by timed arteriography and the muscle irritability by a special device ("Muscle Meter"). The cases could be divided into four groups.

In the first group were patients in whom the arteriogram showed no abnormalities of the vascular wall and both circulation time and reflex tone were normal. A second group consisted of cases with no abnormality in the arteriogram, but with decreased velocity of blood flow and with increased muscular irritability in the affected leg, considered by the authors to indicate a disturbance of the vasoneurotic regulation of the flow in the terminal vascular area, including the arterioles. A third group revealed similar alterations of circulation time and muscle tone and showed, in addition, evidence of organic involvement of the vascular wall in the arteriogram, due to the development of secondary arteriosclerosis. In a last group of patients, who, in the presence of abnormal arteriograms, had a normal circulation time as well as normal muscular tone in the affected extremities, the impairment of circulation was ascribed to an organic vascular lesion without any functional component.

PICK

Burton, A. C.: On the Physical Equilibrium of Small Blood Vessels. Am. J. Physiol. **164**: 319 (Feb.), 1951.

Knowledge of the factors operating to maintain a vessel in a certain diameter under any given blood pressure and vascular "tone" are fundamental to an understanding of small blood vessels. Two forces are in equilibrium in the wall of the vessel. Hydrostatic pressure acts at right angles to the vessel wall to increase its diameter. Opposed to this is the tension *in* the wall of the vessel, acting at a tangent to the radius, to decrease its diameter. This tension may be considered in absolute units (dynes) for unit length of vessel. This force will pull apart the two edges of a longitudinal slit made through the vessel wall. The equilibrium of forces in the wall of a blood vessel is governed by Laplace's law which states that the excess of hydrostatic pressure within the vessel over that outside (dynes per cm^2) is equivalent to the tension in the wall (dynes. per cm.) divided by the radius (cm.).

The total tension of the wall is made up of elastic and active tensions. Elastic tension is due mostly to stretch of elastic fibers in the vessel wall opposing stretch. This tension is determined by the increase in circumference beyond the unstretched value. Tension of smooth muscle due to stretch is considered to be elastic. Active tension depends on contraction of smooth muscle in vessel walls, governed by nervous or humoral factors. Interfacial tension between liquid and vessel wall also plays a role in total tension.

From the radius of blood vessels and the known pressure within them, the total tension in many mammalian vessels has been computed from Laplace's equation, $T = P \times R$. Radius is the most

important factor determining the total tension in the wall since it changes by a factor of 10,000 between aorta and capillaries as compared to pressure which changes about four times. Although pressure falls from capillaries to veins, tensions in the wall rise because the radius increases so much. Elastic fibers in vessel walls and maintenance tensions are well correlated. This permits walls to hold against prevailing blood pressures without continuous energy cost. Because of their small radius, capillaries need no great strength to stand pressures as high as arterial in occlusion experiments.

Elastic diagrams (tension in vessel wall plotted against radius) demonstrate that elasticity follows Hooke's law (a straight line) for only small amounts of stretch, becoming steeper when stretch increases. The linear part is considered to be due to elastic fibers and the steeper part to the restricting jacket of fibrous tissue which limits distensibility when distension is great. With age the linear part has a smaller slope (elastic fibers weakened) and later steeper part appears at smaller degrees of stretch (fibrous wall more important).

Equilibrium can be stable under elastic tension alone but not under active tension alone. Under active tension alone the vessel will either expand progressively in an explosive manner or be completely closed. These facts are shown by equilibrium diagrams which relate the total tension to elastic curves. Intersection of the straight line for total tension and the curve for elastic tension establishes the equilibrium point under elastic tension alone. Elastic tissue is needed to make possible a graded constriction or dilation under vasomotor tone (active tension). Elastic tissue automatically changes tension to a greater extent than required by Laplace's law with change in radius. As in sphincters, where there is little or no elastic tissue, vessels are either opened or closed. Equilibrium, under both elastic and active tensions together, is possible over a range of diameters.

Large increases in active tension are required to produce first constrictions. Slight further increases greatly increase the degree of constriction. The maximum increase in active tension occurs near where elastic tension is zero, that is, any active tension greater than maximum will close the vessel. With a given active tension, if the pressure in the vessel be lowered, the vessel will eventually reach a point where it will have to close completely. This is the "critical closing pressure" which exists for any given active tension. Whenever pressure falls below this point the vessel will close completely. Critical closing pressure (P_c) is the active tension (T_c) in the wall divided by the "unstretched" radius of the vessel (R_0). If the radius of a vessel is known the critical closing pressure will be a measure of the active tension in the wall, the vasomotor tone. Critical closing pressures are independent of blood viscosity.

Important concepts relating to aortic aneurysm and kidney in hypotensive shock are presented. Critical closing pressures above 100 mm. Hg, due to vasomotor tone, have been measured.

OPPENHEIMER

Kral, V. A.: Neuropsychiatric Sequelae of Cardiac Arrest during Spinal Anesthesia. Canad. M. A. J. **64:** 138 (Feb.), 1951.

The author presents the case of an 18 year old boy who suffered cardiac arrest for four and one-half minutes during spinal anesthesia; he discusses in detail the results of neuropsychiatric observation of one year's duration. Immediately after the circulatory arrest was terminated by heart massage and procaine injection, a state of decerebrate rigidity developed. This lasted for 48 hours and was followed by a state of decortication. In the second month of the illness definite signs of cortical function became manifest. However, three months after the cardiac arrest occurred there were signs pointing to involvement of the basal ganglions, the cerebellum and the cervical part of the spinal cord. There was also damage of the pyramidal tract and the sleep regulating apparatus in the diencephalon. Severe cortical damage was reflected in the psychiatric symptoms.

During the ensuing period of observation the patient was apparently able to overcome the damage of the spinal cord and the lower parts of the brain, but a considerable loss of cortical function remained unchanged and there was no appreciable sign of further recovery.

SCHWARTZ

Wagstaff, J. K.: Recurrent Syncopal Attacks from Bradycardia in an Infant. Brit. M. J. **4707:** 614 (March 24), 1951.

The author presents a case in which recurrent attacks of bradycardia and syncope occurred in an infant of 2 months in which the etiology remained obscure. Unconsciousness was followed by asystole with no electrical activity for a few seconds, followed by a regular rate of 37 per minute, which progressively increased with return to normal. The author feels that these attacks simulate cardiodepressor syncope (vagovagal). Adrenaline failed to prevent slowing, but this was probably due to inadequate dosage. Cessation of attacks occurred after quinidine, but this may have been fortuitous or may have been effected through its action in reducing the excitability of the vagal endings. The author concludes that further study may yield information which would classify cases such as this as one of the causes for sudden death in infancy.

TANDOWSKY

Hall, C. E., and Hall, O.: Hypertensive Disease Produced by Desoxycorticosterone Acetate in

Parabiotic Rats. Arch. Path. **51**: 249 (March), 1951.

The authors implanted 100 mg. desoxycorticosterone acetate (DCA) (pellets) in the right partner of 20 pairs of parabiotic rats. After 30 to 40 days the rats were sacrificed. In the interim their blood pressure was recorded at 48 hour intervals. In 75 per cent (15 pairs) the treated rat showed no hypertension. In fact, a hypotension ultimately developed. The untreated partner became hypertensive and microscopic examination revealed arteriolar and parenchymal changes characteristic of DCA hypertension. In the remaining five pairs, in which the treated rat was moderately hypertensive and the untreated remained normal, the vascular union was unsatisfactory. The authors offer no explanation for the peculiarly contrasting results, namely, hypotension in the majority of the treated parabiotic rats and hypertension in the untreated partners.

GOULEY

Henry, J. P., Gauer, O. H., Kety, S. S., and Kramer, K.: Factors Maintaining Cerebral Circulation during Gravitational Stress. J. Clin. Investigation **30**: 292 (March), 1951.

If the blood supply to the human brain is suddenly interrupted, consciousness is lost in six seconds. The circulation should, theoretically, be halted by an acceleration which reduces mean arterial pressure at the level of the head to near zero values. However, maintenance of consciousness has been reported during a blackout. To study this problem further arterial and cerebral pressure and oxygen determinations were made in three subjects during acceleration.

In spite of great falls in cerebral arterial pressure the venous saturation remained almost unchanged. This suggested that cerebral blood flow was being maintained. There was some evidence of active cerebral vasodilatation during acceleration. When a subject is placed in the erect position in a high gravitational field, cerebral vascular sufficiency may be maintained in spite of a great fall in arterial pressure. This may result from a decrease in pressure on the venous side of the cerebral capillaries, or from passive vasodilatation due to an expansion of the cerebral vascular bed. It is probable that whenever acceleration persists for more than a few seconds a combination of these effects develop together with some active cerebral vasodilatation.

WAIFE

Cohen, S. G., Franke, F. R., and Karlson, E. L.: Studies on the Mechanism of Fatal Anaphylaxis in the Rabbit. J. Allergy **22**: 160 (March), 1951.

The authors recorded intracardiac pressure together with electrocardiographic and pneumographic studies during anaphylactic shock. Following the intravenous shocking dose of antigen to sensitized rabbits, the systolic and diastolic right ventricular pressures rose. This was followed by gradual reduction in pressure to zero. In all but one rabbit, respirations ceased abruptly although heart action and intracardiac pressure pulsations continued for periods up to 10 minutes. The abrupt manner in which respiration stopped following the anaphylactic reaction suggests a sudden peripheral respiratory failure. Major electrocardiographic changes did not occur until after respirations had ceased and until after right ventricular pressure changes were no longer recorded. This suggests that death was not due to disturbances in conduction mechanisms of the heart or to myocardial damage.

WAIFE

Tedeschi, C. G., and Stevenson, T. D.: Interstitial Myocarditis in Children. New England J. Med. **244**: 352 (March 8), 1951.

Two cases of interstitial myocarditis in children are presented and the literature of the subject is reviewed. The first case was that of an 11 month old female with clinical signs of an upper respiratory infection and the second that of a 6 week old boy whose outstanding symptoms were those of a gastrointestinal disorder. Both cases showed exudative inflammatory changes involving the endocardium and epicardium as well as the myocardium. Although both cases had an interstitial pneumonic process, no definite causative agent was demonstrated. The authors conclude that "isolated myocarditis" in children is a manifestation of a more generalized disease process which under certain circumstances may lead to severe myocardial complications.

SAGALL

Culbertson, J. W., Wilkins, R. W., Ingelfinger, F. J., and Bradley, S. E.: The Effect of the Upright Posture upon Hepatic Blood Flow in Normotensive and Hypertensive Subjects. J. Clin. Investigation **30**: 305 (March), 1951.

The effect of posture on hepatic blood flow was estimated by the bromsulfalein extraction method in eight normotensive and 12 hypertensive subjects. In all subjects the estimated hepatic blood flow decreased following the tilt from the horizontal to the upright position. This was not associated with proportionate changes in mean arterial pressure so that the calculated hepatic-portal resistance was increased. These changes were not directly related to increases in pulse rate or to other signs or symptoms of poor circulatory adaptation to the upright position. These results confirm the impression gained from indirect evidence, that active vasoconstriction occurs in splanchnic organs when subjects are tilted into the upright position.

WAIFE

Scheinberg, P.: Cerebral Blood Flow and Metabolism in Pernicious Anemia. Blood **6:** 213 (March), 1951.

Cerebral blood flow and metabolism were measured in 16 patients with pernicious anemia. In a group with severe anemia, cerebral blood flow was increased and cerebral vascular resistance decreased; in the group with moderate or no anemia, cerebral blood flow was decreased and vascular resistance increased. In both groups, cerebral oxygen and glucose consumption was decreased, as was cerebral venous oxygen tension. There was a good correlation between the mental status defects and cerebral oxygen consumption and between severity of neurologic involvement and cerebral oxygen consumption. Specific therapy resulted in a moderate increase in cerebral oxygen consumption and cerebrovascular resistance. In no instance did cerebral oxygen consumption become normal. It is concluded that pernicious anemia results in specific nervous system involvement not related to the anemia, and that this damage is at least partially irreversible in many patients.

BERNSTEIN

Nicholson, J. W., Burchell, H. B., and Wood, E. H.: A Method for the Continuous Recording of Evans Blue Dye Curves in Arterial Blood, and its Application to the Diagnosis of Cardiovascular Abnormalities. J. Lab. & Clin. Med. **37:** 353 (March), 1951.

The method of continuous measurement of the concentration of intravenously injected Evans blue dye in whole arterial blood by means of an earpiece oximeter or a cuvette oximeter for whole blood has revealed abnormal patterns in the dye curves obtained in the study of patients who have certain types of cardiovascular disorders.

Artefacts can produce abnormal patterns and can be caused by: (1) electrical or mechanical instability of the recording instruments, (2) failure to deliver the dye to the heart in a uniform manner, and (3) irregularities of respiration, heart rate, cardiac output or rate of blood flow past the oximeters.

A given dye curve may fall into one of five general patterns: (1) the normal pattern, (2) the heart failure pattern, (3) the pattern of left to right shunt, (4) the pattern of right to left shunt, and (5) the combination of left to right with a right to left shunt.

To date reliable anatomic localization of a congenital lesion has not been possible. Cardiac catheterization or some other procedure must be employed to permit this important differentiation. The dye method may have increasing usefulness as a screening procedure and thus render some diagnostic catheterizations unnecessary. The finding of a normal dye curve can rule out the presence of large shunts and likewise, the finding of an unsuspected abnormal curve may be an indication for catheterization of the heart, with the eventual possibility of surgical benefit. The procedure may be a possible method for following the course of cardiac failure or the changes in blood flow resulting from surgery on the heart and great vessels. Quantitative studies may find clinical application in the simultaneous determination of circulation time, cardiac output and Evans blue space in a variety of conditions affecting the circulation.

MINTZ

Eichna, L. W., Berger, A. R., Rader, B., and Becker, W. H.: The Comparison of Intracardiac and Intravascular Temperatures with Rectal Temperatures in Man. J. Clin. Investigation **30:** 353 (April), 1951.

By use of a thermocouple threaded to the tip of an intracardiac catheter temperatures in 24 afebrile subjects were measured potentiometrically. There was a small but consistent gradient of increasing temperature in the larger veins as they approached the heart. The gradient is deeper in the thorax than in the abdomen. Rectal temperature exceeded intracardiac and deep intravascular temperatures by a small but significant amount, while temperatures in the veins draining the liver and brain were higher than the temperatures in the veins into which they drained.

Differences between right heart temperature and rectal temperature were not of sufficient magnitude to be of practical importance in afebrile subjects. During fever, however, rectal temperature may exceed intracardiac temperature by a significant amount. Intracardiac, or its equivalent, femoral arterial, temperature represents an average blood temperature which seems to approach that of the deep tissues more closely than any other single measurement. It would seem that these temperatures would have considerable significance in thermal homeostasis since the temperature of the blood as it enters and affects vital centers in the hypothalamus is more apt to be indicated by these measurements than by any other now available.

WAIFE

Gray, F. D., Jr., Lurie, P. R., and Whittemore, R.: Circulatory Changes in Chronic Pulmonary Disease. A Study of Pulmonary Collateral Circulation. Yale J. Biol & Med. **23:** 380 (April), 1951.

Physiologic studies in cyanotic congenital heart disease and pathologic studies in chronic pulmonary disease have demonstrated the existence of collateral circulation between systemic and pulmonary arteries. These are in the form of pre-capillary anastamoses between bronchial and pulmonary arteries. The authors report studies on 10 patients with chronic lung disease, using the technics of cardiac catheterization and oxygen analyses while breathing room air and oxygen. Estimations of

systemic blood flow, shunted blood flows and effective pulmonary flow were made according to formulas which are discussed in this report.

In 7 of the 10 cases, mixed venous blood was being shunted through nonaerated lung capillaries, and in each of these cases evidence was obtained indicating the presence of collateral channels between bronchial and pulmonary arteries. Two of these cases came to surgery, and the resected lung specimens supported the estimations of collateral flow.

In chronic lung disease the development of collateral flow cannot be ascribed to a high pressure gradient between systemic and pulmonary circulations, but is probably due to chronic inflammation. Since the collateral circulation develops in diseased parts of lung where further aeration is poor, it results in relatively slight benefit at the expense of an increased work load on the left heart, which may then fail. This mechanism is an important factor in the paradoxic observations of left ventricular hypertrophy reported in cases of cor pulmonale and cardiopulmonary disease.

ENSELBERG

Robertson, J. A., Gray, C. H., and Baynes, A. H.: Renal Function in Diabetic Nephropathy. Arch. Int. Med. **87**: 570 (April), 1951.

Nine diabetic patients on clinical grounds were diagnosed as suffering from the specific renal lesion described by Kimmelsteil and Wilson. Two of these diagnoses have subsequently been confirmed at autopsy. The inulin clearance, paraaminohippurate clearance, maximum tubular reabsorptive capacity and maximum paraaminohippurate tubular excretory capacity have been measured in these patients, and the results are discussed.

These investigations were initiated in the hope that in diabetic glomerulosclerosis a characteristic pattern of disturbance of the various renal functions susceptible of measurement would, on the one hand, facilitate the diagnosis of the condition during life by means of special tests and, on the other hand, further knowledge concerning the pathogenesis of the condition. The results of this brief series of investigations show that the first hope has not been realized. The pattern of disturbance of renal function closely resembles that observed in chronic nephritis, and, while more refined statistical analysis of a much larger series of cases may reveal subtle differences between the disturbances of functions resulting from these two lesions, this will not be of any value in the diagnosis of the individual case.

The results throw no light on the pathogenesis of this condition. These renal function tests do not provide during life a means of differentiating the condition from nonspecific renal disease in diabetics.

BERNSTEIN

Hickam, J. B., and Pryor, W. W.: Cardiac Output in Postural Hypotension. J. Clin. Investigation **30**: 401 (April), 1951.

The effect of tilting on the cardiac output was studied in 12 patients with postural hypotension. Cardiac outputs were determined following intracardiac catheterization. A significant fall in blood pressure was more consistently associated with a failure of normal arteriolar constriction than with abnormal declines in cardiac output. Subjects with significant postural hypotension on tilting revealed a very minor increase in peripheral resistance, or an actual fall. The postural fall in cardiac output was variable. It was found that significant postural hypotension can occur without a greater than normal fall in cardiac output, and that a very large fall in cardiac output can occur without a significant drop in blood pressure.

Large infusions of human serum albumin, in five cases, led to an increase in cardiac output in the tilted position.

The authors suggest that postural hypotension is primarily dependent upon inadequate arteriolar tone in the upright position.

WAIFE

McCord, M. C., and Taguchi, J. T.: Nonspecific Pericarditis. Arch. Int. Med. **87**: 747 (May), 1951.

A case of nonspecific pericarditis with a fatal termination is presented. The probable harmful effect of anticoagulant therapy is considered.

The difficulty in differentiating acute nonspecific pericarditis from acute myocardial infarction is shown quite clearly. Many of the classic features of myocardial infarction were present. The patient was in an older age group; the onset, location and radiation of pain were typical; fever and leukocytosis were present; and a friction rub developed. In retrospect it was seen that the significant points suggesting the presence of pericarditis were the relation of the pain in the chest to respiration, the constancy, duration and intensity of the friction rub and the failure of development of electrocardiographic changes suggesting myocardial infarction.

Postmortem examination unequivocally established the primary disease as being in the pericardium and showed intense hemorrhagic changes with an element of cardiac tamponade. In the reported cases of benign pericarditis in which pericardicentesis was performed, the large majority revealed hemorrhagic fluid. It seems probable that in such instances anticoagulant therapy would intensify bleeding into the pericardial sac. The supposition that this above case terminated fatally in part owing to the anticoagulant therapy appears justifiable.

BERNSTEIN

Freis, E. D., Stanton, J. R., Finnerty, F. A., Jr., Schnader, H. W., Johnson, R. L., and Wilkins, R. W.: The Collapse Produced by Venous Congestion of the Extremities or Venesection Following Certain Hypotensive Agents. J. Clin. Investigation **30**: 435 (May), 1951.

Peripheral collapse may occur during venous congestion of the extremities in normal subjects and in those who suffered recent blood loss. Patients receiving hypotensive agents, such as sodium nitrite, mixed dihydrogenated alkaloids of ergot, or hexamethonium, and to some extent tetraethylammonium, are unusually susceptible to this "congestion-collapse." Hypotensive drugs such as veratrum viride and sodium amytal, which do not ordinarily cause postural hypotension, did not induce congestion collapse.

Measurements of the blood volume trapped in the limbs indicate that this hypotension and collapse is not due to pooling of excessive amounts of blood in the limbs. This reaction is probably due to failure of compensatory vasoconstriction in other areas than in the congested extremities.

Sympathectomized subjects were more resistant to hypotension during the post-drug period than normal subjects.

WAIFE

Lagercrantz, R.: The Role of Antistreptolysin in Scarlet Fever and Some Other Infectious Diseases. Scand. J. Clin. & Lab. Investigation. **2**: 152 (fasc. 2), 1951.

Antistreptolysin titers were determined weekly for three to seven weeks in several hundred cases. The titers started increasing in the first week of the disease and became maximal in three to seven weeks. Young children generally had higher titers than adults, and also had a higher frequency of suppurative complications and a lower frequency of myocarditis than adults. A significant correlation was found between prolonged initial fever and higher antistreptolysin values. Penicillin treatment tended to inhibit antistreptolysin production, reflected also in the increased frequency of relapse in penicillin-treated cases. Patients with suppurative complications produced more antistreptolysin than did uncomplicated cases. The highest titers observed occurred in the cases of acute nephritis.

ENSELBERG

PATHOLOGY

Collier, F. C., and Rosahn, P. D.: Endocardial Fibroelastosis. Pediat. **7**: 175 (Feb.), 1951.

Of 205 autopsies on infants under two years, there were two instances of congenital fibroelastosis of the endocardium. The authors reviewed 11 previously reported cases and added two new cases. Twelve were under 27 months and nine under 5 months of age. The presence of fibroelastic thickening of the endocardium in one premature infant suggests that the pathogenesis may be operative in early fetal life. Cardiac hypertrophy was observed in all but one case. All of the patients died in cardiac failure. Seven of the 13 cases had associated cardiovascular anomalies besides cardiac dilatation or hypertrophy. The abnormalities in five cases were located in the great vessels of the heart, and the remaining two cases had anomalies of the heart chambers. Fibroelastic thickening of the left ventricle was observed in all of the cases. Ten showed the changes in both the left ventricle and the left auricle, and one showed endocardial thickening in both ventricles and in the right auricle. There was a history of infection during pregnancy in five cases. However, on both gross and microscopic examination there was no evidence of an inflammatory anlage in the production of these lesions. Although the pathogenesis of this lesion is not definitely known, the authors believe that the explanation probably lies in a developmental aberration in the fetus.

MARGOLIES

Weinstein, L., and Shelokov, A.: Cardiovascular Manifestations in Acute Poliomyelitis. New England J. Med. **244**: 281 (Feb. 22), 1951.

The authors' observations of 428 patients with poliomyelitis are reported. Fifty per cent of the patients were adults. Electrocardiograms were recorded in 28 patients; 11 showed abnormalities in the T waves, prolongation of the P-R or Q-T intervals, depression of the RS-T segments, or a Q_3T_3 pattern. One patient with a Q_1T_1 pattern had acute myocarditis at autopsy. The electrocardiograms became normal in those patients who recovered. Seven per cent of the patients had prolonged hypertension during the acute illness. This was more common in those individuals over age 16 years and in those who were cyanotic and severely ill. The authors believe suboxygenation is the cause of hypertension in most of these cases and they were able to relieve it by administration of oxygen or by improving respiratory efficiency mechanically or both. Acute pulmonary edema was common in fatal cases of the bulbar form of poliomyelitis and it is suggested that intravenous fluids are best avoided. Since all cases with pulmonary edema were of the bulbar type, the authors consider a central origin for the edema most probable, but disease of the myocardium may have been a contributing factor in some instances. Myocarditis was present in 12 of the 16 patients who were examined at autopsy. One showed focal edema of the mitral valve, another had hemorrhage into the mitral valve, and a third had a sterile acute pericarditis. Myocarditis seemed more common and it was more severe in the older patients. The presence of myocarditis is considered evidence suggesting that poliomyelitis may produce damage in structures outside the nervous system.

ROSENBAUM

Kisch, B., and Bardet, J. M.: Electron-Histology of the Heart Elements of the Heart and Blood of the Mouse. Exper. Med. & Surg. **9:** 1 (Feb.), 1951.

Owing to the higher resolving power of the electron microscope the authors were able to see details that have not been reported in the literature. (1) The nuclei found in the newborn mouse heart are of greater number and more elongated than those found in the adult mouse heart. The nuclei contain more than one nucleolus, as a rule. (2) Two types of fibrils were differentiated in the heart muscle. Type A is cylindrical with regular segmentations, resembling a bamboo stick. These fibrils are characteristically connected only at the intersections, corresponding to the Z band of the skeletal muscle fibril. Between two of these intersections, forming the border lines of a sarcomere and parallel to them, a dark line or two small dark lines separated by a light area can be seen. These lines are the equivalent of the M band of striated muscle. Type B of the muscle fibers of the heart has a typical syncytial character. They do not present continuous single fibrils, but for a short distance a fibril can be seen before it merges with its neighbor. Z lines cross the entire width of these sheaths and in some areas broader dark lines exist perpendicular to the Z lines. (3) Capillaries are easily recognized. They have a dark endothelial lining. The endothelial nuclei are flat or curved and covered by an endothelial sheath. Some of them contained nucleoli. (4) The blood corpuscles were not circular but of a crescent or sausage outline and depending on the direction of the cut, they had the form of a ring or doughnut. The largest circularly shaped red blood cell had a diameter of about 4.5 to 5 microns. Occasionally spindle shaped cells 2.0 to 2.5 microns long and 0.5 microns wide were observed; these were regarded as thrombocytes. (5) The arrangement of the fibrils of striated muscle from the abdominal rectus muscle of mice showed a similarity to the arrangement of the bamboo stick fibrils of the auricle and ventricle. These fibrils are connected with each other in the region of the Z bands, in a warp and woof pattern.

GELFAND

Nadas, A. S., Alimuring, M. M., and Sieracki, L. A.: Cardiac Manifestations of Friedreich's Ataxia. New England J. Med. **244:** 239 (Feb.), 1951.

Six cases of Friedreich's disease are described. Four were males and two were females. Only one patient had symptoms referable to the circulation, consisting of congestive heart failure, parasystole and pericardial effusion with development later of pain suggestive of angina pectoris. Cardiac enlargement was present in three cases and cardiac murmurs in five. The electrocardiograms were abnormal in all of the five patients in whom they were recorded. The major electrocardiographic changes were: inversion of the T waves in two or three of the standard leads, lead aV_F, and in leads from the left precordium (leads V_5 and V_6). In one case postmortem studies revealed diffuse myocardial fibrosis and extensive coronary arterial obstruction, chiefly in the left ventricle. No explanation for the arterial change is offered, but it is speculated that examination of skeletal muscle in these cases may show similar vascular changes. Electrocardiographic studies may be helpful in the diagnosis of suspected cases of Friedreich's disease where the chief complaint is incoordination. An abnormal electrocardiogram tends to establish the diagnosis in such cases but a normal record does not exclude Friedreich's ataxia.

ROSENBAUM

Gross, S. W.: Spontaneous Occlusion of the Internal Carotid Artery in the Neck. J. Mt. Sinai Hosp. **17:** 746 (March–April), 1951.

Spontaneous occlusion of the cervical portion of the internal carotid artery may be a rare cause of the sudden occurrence of hemiplegia. It is difficult or impossible to differentiate between pulsation of the internal and external carotid arteries by palpation, but the internal carotid artery is larger than the external, so that an absence of pulsation or a marked difference in the carotid pulses above the bifurcation on the two sides should arouse a suspicion that occlusion of the internal carotid artery might exist. It may occur during early adult life, but atherosclerosis is the most common cause. Syphilitic arteritis, nonspecific arteritis, and embolism may also result in acute vascular occlusion of the carotid vessels in the neck.

The author presents two cases, both of whom had developed sudden hemiplegia, presumably on the basis of a cerebrovascular accident. Study some months later revealed occlusion of the internal carotid artery. In one case, the thrombosed segment was resected and it showed marked arteriosclerotic narrowing with an organizing thrombotic occlusion.

CORTELL

Saphir, O., and Lowenthal, M.: Changes in the Endocardium of Pigs Simulating the Rheumatic Stigmata of Man. Am. J. Path. **27:** 211 (March–April), 1951.

The authors examined 1000 pig hearts grossly and 850 additional hearts microscopically. In the first group, 200 were from pigs under 8 months of age, and showed no evidence of endocarditis. The older group showed 12 instances of recent endocarditis, featured by edematous and hemorrhagic valvular infiltration; eight cases of acute vegetative endocarditis, in two of which bacteriologic study proved the causative factor to be *Eresipelothrix rhusiopathiae*.

In the group of 850 porcine hearts microscopically examined, numerous chronic changes were noted in approximately 10 per cent, involving the mitral

valve leaflets, small musculoelastic arteries, the myocardium and the pericardium, and of a type closely resembling those lesions in chronic rheumatic heart disease generally labeled as "rheumatic stigmata." These constitute the minor histopathologic findings commonly noted in chronic rheumatic heart disease as contrasted with the specific Aschoff changes and sometimes used in the absence of the latter as the diagnostic basis in cases of atypical valvular pathology. Multiplication, distortion and calcification of the elastic structure, subendocardial fibrosis and cellular "palisade" are commonly seen in pig hearts, in the mitral valve and in the left auricle. This suggests to Saphir and Lowenthal that pigs have a chronic endocarditis residual from bacterial and vegetative endocarditis indistinguishable in the healed state from what commonly is accepted as chronic rheumatic heart disease in the human. The authors believe that many human hearts with moderate valvular fibrosis and without Aschoff bodies but showing "rheumatic stigmata" may thus be evidence of healed bacterial endocarditis rather than rheumatic fever.

GOULEY

Pariser, S., Zuckner, J., Taylor, H. K., and Messinger, W. J.: Mitral Stenosis without Clinically Demonstrable Left Auricular Enlargement. Am. J. M. Sc. **221:** 431 (April), 1951.

The demonstration of an enlarged left auricle by radiologic examination has been considered an important criterion in support of the diagnosis of mitral stenosis. In a survey of the clinical material available to the authors, seven patients out of 30 with this disease failed to demonstrate the roentgen characteristics of left auricular enlargement, either by fluoroscopy or esophagograms. This problem was further studied in a review of the records of 30 patients with mitral stenosis and left auricular enlargement found at autopsy following a period of clinical observation. In six cases, no evidence of left auricular enlargement had been discerned ante mortem. In one instance a giant left auricle was suspected despite normal esophagograms because of a double contour visible along the right cardiac border. In four of the six cases with unrecognized auricular enlargement, aortic valve lesions were found in association with mitral stenosis. In the entire study, there were 13 patients in whom left auricular enlargement was not radiologically demonstrable; in 11 of these patients, auricular fibrillation was present. It is concluded that mitral stenosis may exist without roentgen evidence of enlargement of the left auricle.

SHUMAN

Hirst, A. E., Jr., and Affeldt, J.: Abdominal Aortic Aneurysm with Rupture Into The Duodenum. Gastroenterology **17:** 504, (April), 1951.

Eight cases of abdominal aortic aneurysm which ruptured into the duodenum were found in 16,633 autopsied cases. Seven cases were arteriosclerotic in origin and one combined severe arteriosclerotic with syphilitic changes. The average age was 72 with a range from 66 to 80 years. The ratio of men to women was 5:3. Occupation was not important etiologically. Four patients had hypertension. Abdominal pain, continuous, burning or colicky, and unrelated to meals, was present in seven cases. It was epigastric in location and referred to the back in three cases. It was relieved by sitting up in two cases. The pain was usually a terminal manifestation and preceded melena and hematemesis by only a short period in all but two cases. Two patients had syncope, though weakness was noted by all; two noted an abdominal mass, one for 30 years and one for 19 months; two had weight loss. Physical examination was negative except for an abdominal mass in seven cases.

X-rays showed vertebral erosion with sparing of the discs; a soft tissue mass with organ displacement; calcification, when present, was thin and crescentic with the concavity toward the vertebral column.

The prognosis is poor.

BERNSTEIN

PHARMACOLOGY

Rennie, J. B., Milne, J. A., and Sommerville, J.: Trial of a Cinchoninic Acid Derivative in Some Collagen Diseases. Brit. M. J. **4703:** 383 (Feb. 24), 1951.

A cinchoninic acid derivative, 3-hydroxy-2-phenylcinchoninic acid (HPC), has been used in a small series of patients. Fever and acute arthritis were speedily relieved in rheumatic fever. Results in polyarteritis nodosa were equivocal.

The most striking effects in the series were obtained in three patients with scleroderma, a disease hitherto not responsive to any known treatment. Improvement occurred in all cases, as shown by the histologic examination of biopsy specimens obtained before and after treatment. The results were striking and have so far been maintained in one case, but were only temporary in two.

Very slight and inconstant improvement followed the administration of HPC in chronic lupus erythematosus, but was not confirmed by histologic examination. Toxic effects were infrequent and less severe than those which may follow the use of sodium salicylate, and consisted in slight nausea, diarrhea and, more rarely, vomiting.

BERNSTEIN

Iron, E. N., Ayer, J. P., Brown, R. G., and Armstrong, S. H., Jr.: ACTH and Cortisone in Diffuse Collagen Disease and Chronic Dermatoses. J.A.M.A. **145:** 861 (March 24), 1951.

Eight cases of disseminated lupus erythematosus, two cases of deep-seated exfoliative dermatitis, and one case each of periarteritis nodosa, scleroderma, discoid lupus erythematosus, superficial allergic dermatitis, and dermatitis herpetiformis, were chosen

for treatment. The aim of the study was to contrast the effect of cortisone and ACTH with respect to therapeutic response using the skin for detailed histologic control. Of the 10 patients with disseminated collagen disease in this study, six were critically ill and the other four were progressively deteriorating. During the study one of these patients, who was seriously ill with disseminated lupus erythematosus, died on the third day of treatment while receiving cortisone. In disseminated lupus it was noted that ACTH appears to have induced faster remissions, but because of the high incidence of complications on long term ACTH therapy, remissions, once obtained, appeared best held on cortisone. In certain chronic dermatoses cortisone appears to be without effect in contrast with the striking healing effect of ACTH. The problems of management of the serious complications of long term therapy are discussed. The authors conclude that short term therapy, two weeks or under, with ACTH can be carried out safely under a proper regimen without extensive laboratory control, but long term therapy with this hormone demands the availability of the laboratory. Long term cortisone therapy because of diminished incidence and severity of complications is more subject to general use. No instance of permanent cure in any of these conditions was observed though in several cases therapy appeared life-saving.

KITCHELL

Kjerulf-Jensen, K., Krarup, N. B., and Warnung-Larsen, A.: Persistent Hypokalemia Requiring Constant Potassium Therapy. Lancet **260**: 372 (Feb. 17), 1951.

A woman of 33, who had had lymphocytic meningitis five years before, developed severe anorexia and muscular weakness after an attack of peritonsillitis and a six-month abortion. She was at first thought to have Addison's disease, but treatment with sodium chloride and desoxycortone produced severe cardiac disturbances and she was then found to have a very low serum potassium level. Her hypokalemia and weakness lasted for six months and could only be relieved by giving potassium phosphate regularly by mouth, her condition relapsing whenever the potassium therapy was discontinued.

It is important to recognize that such cases exist; that the condition may be hard to differentiate from Addison's disease, anorexia nervosa, and familial periodic muscular paralysis; and that potassium by mouth will relieve all the symptoms of hypokalemia over long periods and may be life saving.

BERNSTEIN

Davidsen, H. G., Kjerulf-Jensen, K., and Krarup, N. B.: Treatment of Chronic Renal Potassium Deficiency. Lancet **260**: 375, (Feb. 17), 1951.

Acute hypokalemia developed in a woman of 44 with chronic kidney disease. It was combated successfully with parenteral and oral potassium salts. In four days the patient retained 1072 mEq. of potassium and was dramatically relieved.

The administration of neutral potassium phosphate caused hyperphosphatemia and hypocalcemia, with temporary tetany and inhibition of blood-clotting. The administration of a concentrated solution of potassium chloride without a simultaneous supply of phosphate reduced the serum phosphate to zero. There were no demonstrable changes in serum calcium.

The authors found that in normal rabbits the administration of sodium phosphate lowered the serum calcium while the serum potassium remained constant. The infusion of potassium chloride solution in normal rabbits did not lower the serum phosphate. These findings agree with the concept that the fall in serum phosphate is intimately connected with the assimilation of potassium by the potassium deficient cells.

BERNSTEIN

Falk, A., and Ebert, R. V.: Tuberculous Pericarditis Treated with Streptomycin. J.A.M.A. **145**: 310 (Feb. 3), 1951.

Seventeen patients with tuberculous pericardial effusion and associated circulatory failure were treated primarily with streptomycin. Forty-seven per cent improved; 35 per cent of the patients died. Seven cases had pericardiectomies with only one death. No spread of tuberculosis was noted following operation in any case previously treated with streptomycin. These results are good in comparison with a series of 18 patients not receiving streptomycin, of which two improved with medical management alone and the remaining six survivors improved only after pericardiectomy.

KITCHELL

Holley, H. L., and McLester, J. S.: Salt Depletion Syndrome Associated with Decompensated Cirrhosis of the Liver. J.A.M.A. **145**: 392 (Feb. 10), 1951.

Two cases of cirrhosis of the liver with ascites were put on salt-free diets and weekly injections of mercurial diuretics. After failure of improvement on this regime abdominal paracentesis was done. Following this each patient developed a salt-depletion syndrome. The authors feel this may explain the disastrous results that sometimes follow repeated removal of large amounts of ascitic fluid after the use of salt-free diets and mercurial diuretics.

KITCHELL

Levitan, B. A.: Clinical Observations on the Effects of Injectable Rutin, Esculin, Adrenoxyl, and Vitamin E on the Capillary Fragility of Diabetic Retinopathy. Am. J. M. Sc. **221**: 185 (Feb.), 1951.

Oral therapy with rutin for control of capillary

fragility has been generally considered of no value in diabetes mellitus. In order to avoid difficulties with intestinal absorption during oral administration, rutin was prepared for intravenous injection as a methyl glucamine complex. In addition, two other types of "Vitamin P", Esculin and Adrenoxyl, were investigated for their capillary stabilizing effects. Vitamin E was also studied for its ability to influence capillary fragility. The drugs were administered parenterally and orally to a series of diabetic patients. Petechial counts were performed using a positive pressure method.

None of the agents employed singly or in combination had any significant influence upon increased capillary fragility. Spontaneous variations in the response to tests for capillary fragility were encountered in diabetes. It is pointed out that the adrenal steroids have a capillary stabilizing effect which may be responsible for such variability.

SHUMAN

Deterling, R. A., Jr., and Apgar, V.: Use of Norepinephrine (*l*-Arterenol) as a Pressor Drug with Special Reference to Thoraco-Lumbar Sympathectomy. Ann. Surg. **133**: 37 (Jan.), 1951.

Norepinephrine is a primary amine identical in chemical formula to epinephrine except for the absence of a methyl group on the nitrogen atom. It has been synthesized and has also been extracted from postganglionic adrenergic nerves, from the adrenal medulla and from pheochromocytomas of man. It may be a possible precursor of epinephrine in the body, although the pharmacologic action of the two drugs varies significantly. Norepinephrine produces a slowing of the heart, a rise in systolic and diastolic pressures and a total increase of peripheral resistance without any significant effect on cardiac output. The latter response is entirely different from that elicited by epinephrine.

The authors used norepinephrine during and following thoracolumbar sympathectomy in an attempt to maintain blood pressure. The drug, given in a continuous intravenous infusion, was found to possess all the actions of a very satisfactory pressor agent.

ABRAMSON

Foster, C. A., and Naylor, P. F. D.: Sensitivity to Mercurial Diuretics. Lancet **260**: 614 (March 17), 1951.

Two cases illustrating a pyrexial reaction to mercurial diuretics are presented. The reactions followed the mercurial injections after about three hours and were characterized by fever up to 104 F., rigors, cyanosis, and cough. These symptoms increased daily and ceased when mercurials were discontinued. Different brands of mercurial drugs with slightly different molecular structure produced identical responses, and oral administration caused fever in one case but no effect on temperature or diuresis in the second. Dimercaprol (BAL) was tried and had no effect, but an insufficient amount seems to have been given before the mercurial administration. Both of the patients showed a heightened reaction to intradermal injections of these drugs as compared with controls.

BERNSTEIN

Kauntze, R., and Trounce, J.: The Hypotensive Action of Veriloid (Veratrum Viride)—A Clinical Investigation. Lancet **260**: 549 (March 10), 1951.

Veriloid is a potent hypotensive drug which on injection rapidly causes a profound fall in blood pressure. For this reason it should prove of value in hypertensive encephalopathy and the convulsions of puerperal eclampsia. Given by mouth its absorption is difficult to control and its effect lasts a relatively short time, with the result that uniform lowering of the blood pressure is not readily obtained; but the variations can be kept at a lower level and symptomatic relief is usually attained. The margin between therapeutic and toxic levels, where high dosage is necessary, is small and makes the fixed arteriosclerotic type of hypertension unsuitable for treatment. Because of vagus action, veriloid is best avoided in the presence of peptic ulceration. Its main field of usefulness is in the younger patients with severe benign or malignant hypertension and possibly those with chronic nephritis.

The toxic effects of veriloid fall into two groups: (1) nausea, vomiting, faintness, and collapse due to its hypotensive action; and (2) bradycardia and substernal and epigastric discomfort from vagal stimulation. Nausea has been produced at times in all the patients, and though this is a nuisance it is also a protection against excessive dosage. The nausea is not invariably the result of hypotension or of vagal stimulation, for it may still occur where neither of these effects is manifest and may then perhaps be central in origin. The patients who developed faintness did so after a considerable amount of veriloid had produced a well marked hypotensive effect, and ephedrine, by abolishing the hypotension, gave immediate relief. The vagal effect is readily overcome by atropine.

BERNSTEIN

Stover, J. H., Jr.: An Electric Defibrillator for Cardiac Resuscitation. U. S. Air Force M. J. **2**: 57 (Jan.), 1951.

The author has designed a defibrillator which consists essentially of an isolating transformer, a current limiting resistor, and a fast-acting electric switch. Additional testing circuits are included, intended primarily for convenience in animal experimentation when it may be desired to change the current. It is claimed that the apparatus is entirely safe and reliable and can deliver 2 amperes on short-circuit test of the electrodes. The author de-

scribes the technical design of the apparatus and its operation in detail.

SCHWARTZ

Heymans, C., De Vleeschhouwer, G. R., and Van Den Heuvel-Heymans, G.: Adrenolytic Drug and Action of Adrenaline and Noradrenaline on Carotid Sinus. Arch. internat. d. pharmacodyn. et d. thérap. **85**: 188 (Jan.), 1951.

Experiments were performed in dogs to investigate the influence of an adrenolytic compound on the actions of adrenaline and noradrenaline on the arteries of the carotid sinus and thus on the general arterial pressure and respiration. The adrenolytic drug was found to reverse the local action of *l*-adrenaline and *l*-noradrenaline on the arterial walls of the carotid sinus.

SCHWARTZ

Stimson, W. H., and McKusick, V. A.: Febrile Reactions to Quinidine. Am. J. M. Sc. **221**: 440 (April), 1951.

The oral administration of quinidine sulphate produced a febrile response in two patients reported by the authors. In one instance, there appeared a maculopapular rash with petechiae and splenomegaly in association with drug fever. Cessation of quinidine therapy was followed by subsidence of the anaphylactoid purpuric and febrile reactions. A later exhibition of quinidine in a single dose of 0.4 Gm. produced an abrupt rise in temperature to 104 F. In the second patient, symptoms of cinchonism accompanied the drug fever, both of which subsided when quinidine was discontinued.

It is noted that the febrile reaction appears several days to a week after quinidine therapy has been started. The fever disappears within a period of several hours after withdrawal of the drug. Subsequent doses will produce fever promptly, indicating an acquired sensitivity to the drug.

SHUMAN

Brown, M. G.: Acute Benign Pericarditis. New England J. Med. **244**: 666 (May 3), 1951.

Thirteen cases of acute benign pericarditis were studied and seven are reported in detail. The ages of the patients ranged from 21 to 53 years. The main symptom was that of substernal or precordial pain lasting hours to days. In most cases the pain was aggravated by a change in position. Additional symptoms of fatigue, cough, dyspnea, or preceding respiratory infection were commonly found. The outstanding physical findings were fever, a pericardial friction rub lasting from hours to several weeks, and cardiac enlargement. All patients showed electrocardiographic changes of elevation of S-T segments and inverted T waves in limb and one or more chest leads. Subsequent examination of all patients one and one-half to three years after the acute illness has not revealed any cardiac symptomatology or abnormal findings.

SAGALL

Cruickshank, A. H., and Mitchell, G. W., Jr.: Myocardial, Hepatic and Renal Damage Resulting from Para-aminobenzoic Acid Therapy. Observations in Human Cases and Experimental Animals. Bull. Johns Hopkins Hosp. **88**: 211 (March), 1951.

Two cases of acute rheumatic fever and one case of possible arthritis in children were treated with paraaminobenzoic acid. All three cases died. At autopsy, marked fatty changes were found in the heart, liver, and kidneys. In view of these findings, an attempt was made to reproduce these lesions experimentaliy. It was found that by giving large doses of paraaminobenzoic acid by stomach tube to rabbits, similar fatty changes were produced in the liver, kidneys and heart of these animals. It was concluded that the use of large doses of paraaminobenzoic acid in therapy is not without danger.

MARGOLIES

Hahn, E. O., Houser, H. B., Rammelkamp, C. H., Jr., Denny, F. W., and Wannamaker, L. W.: Effect of Cortisone on Aucte Streptococcal Infections and Post-Streptococcal Complications. J. Clin. Investigation **30**: 274 (March), 1951.

In a group of 87 treated and 87 control patients at an Air Force Base, cortisone, in the doses used, had no effect on the symptoms or physical signs of acute streptococcal sore throat. Furthermore, fever appeared to be prolonged in those patients receiving cortisone. Cortisone therapy failed to alter appreciably the antistreptolysin response to streptococcal infections.

There were two cases of acute rheumatic fever in the treated group and five cases among the control patients, but this distribution could have occurred by chance.

WAIFE

Gelfand, M. L., and Widlitz, A. R.: The Use of Mercuhydrin in the Recognition of a Cardiac Factor Complicating Bronchial Asthma. Am. J. M. Sc. **221**: 250 (March), 1951.

The effectiveness of mercurial diuretics in the treatment of congestive heart failure suggested to the authors that these agents may be of value in the recognition of this complication occurring in patients known to have asthma. This was investigated in a group of six asthmatic patients, aged 59 to 71 years, who had become resistant to the usual anti-allergic therapy. Emphysema and pulmonary fibrosis were present in all. Hypertension was noted in four patients and arteriosclerosis in the entire group. Because of evidence of cardiac disease, Mercuhydrin was administered, whereupon the previously refractory asthmatic state improved with a complete

subsidence of wheezing, rales, dyspnea, and orthopnea. The patients were maintained subsequently on intermittent mercurial injections in addition to their anti-allergic program with amelioration of the asthmatic paroxysms. A control group of uncomplicated asthmatic patients, aged 25 to 40 years, experienced no benefit from the use of Mercuhydrin. It is suggested from this study that allergic patients over 50 years of age whose symptoms fail to respond to anti-allergic management may have a complicating left ventricular failure which can be differentiated by the use of mercurial diuretics.

SHUMAN

DiPalma, J. R., and Mascatello, A. V.: Analysis of the Actions of Acetylcholine, Atropine, Epinephrine and Quinidine on Heart Muscle of the Cat. J. Pharmacol. & Exper. Therap. **101**: 243 (March), 1951.

The effect of drugs on the auricle and isolated papillary muscle of the cat were studied by an electronic stimulator. Acetylcholine lowered resting excitability by increasing the rheobase and increased excitability at the same time by shortening the chronaxy. Both of these changes were restored to control levels by the addition of atropine. Atropine alone and quinidine decreased resting excitability, while epinephrine increased it. The refractory period was lengthened by atropine and quinidine, and was shortened by acetylcholine and epinephrine. Contractility was increased by epinephrine and decreased by quinidine and by acetylcholine. The effect of acetylcholine was abolished by atropine, but atropine given alone had little effect on contractility. Spontaneous rhythmic contractions of the muscle were always stopped by acetylcholine and restored again by atropine. Atropine given independently, however, either precipitated or made it easier to initiate spontaneous rhythm. Spontaneous activity was nearly always started by epinephrine but not by quinidine.

SAGALL

Webb, J. L., Saunders, P. R., and Nakamura, K.: The Metabolism of the Heart in Relation to Drug Action. VI. Metabolic Actions of Quinidine on Rat Heart Muscle. J. Pharmacol. & Exper. Therap. **101**: 287 (March), 1951.

The oxygen uptake, anaerobic glycolysis, and adenosinetriphosphatase activity of rat heart muscle were studied before and after the addition of quinidine sulfate. From the results obtained the authors believe that the depression of oxidative metabolism of auricular and ventricular muscle may be responsible for the observed pharmacologic actions of quinidine upon heart muscle and that a major site of action of quinidine upon oxygen consumption is upon glycolysis.

SAGALL

Stutzman, J. W., Simon, H., and Maison, G. L.: Role of Vagus Nerves in Depressor Action of Veratrum Derivatives. J. Pharmacol. & Exper. Therap. **101**: 310 (March), 1951.

Intravenous infusion of potent veratrum derivatives (germitrine, protoveratrine, germidine, germerine, veratridine, and veratramine) in anesthetized dogs resulted in hypotension. This response was not altered by bilateral cervical vagotomy. This implies that the hypotensive effect of the veratrum alkaloids is due to a vasodilatation resulting from a central action and not from a reflex via the vagus nerves.

SAGALL

Wégria, R., Nickerson, J. L., Case, R. B., and Holland, J. F.: Effect of Nitroglycerine on the Cardiovascular System of Normal Persons. Am. J. Med. **10**: 414 (April), 1951.

Sublingual administration of nitroglycerin (0.0006 Gm.) produced increased cardiac output per minute, as well as increased systolic output and heart rate, without altering the blood pressure in 10 normal, healthy, young adults. The cardiac output was determined ballistocardiographically in all cases.

In one instance direct cardiac catheterization yielded qualitatively similar results. The authors believe that cardiac work per beat and per minute is increased by nitroglycerin in the dose used and that nitroglycerin relieves the anginal pain of myocardial ischemia by increasing the coronary flow relatively more than the work of the heart. Caution is advised in the use of nitroglycerin if the anginal pain is not caused by simple, temporary, myocardial ischemia since the drug may produce an undesirable increase in the work of an already handicapped myocardium or shock if the myocardial reserve has been too drastically affected by infarction. The mechanism of increased cardiac output, although uncertain, may be produced by the primary action of nitroglycerin in increasing the venous return by opening wider communications between arteries and veins. The vasodilator effect of nitroglycerin may also lead to an ephemeral decrease in blood pressure which increases heart rate and output reflexly via carotid sinus and aortic arch reflexes.

HARRIS

AMERICAN HEART ASSOCIATION, INC.

1775 Broadway, New York 19, N. Y.

Telephone Plaza 7-2045

GRANTS-IN-AID

Applications for American Heart Association Research Grants-in-Aid to qualifying institutions, including grants to basic science studies not directly related to the cardiovascular field, should be filed before the deadline, December 1, 1951. Information and forms may be obtained from the Medical Director.

SCIENTIFIC COUNCIL COMMITTEE

Dr. Howard B. Sprague, Chairman of the Association's Scientific Council, has appointed a Committee under the Chairmanship of Dr. Robert W. Wilkins of Boston to recommend a plan of reorganization for the Council, including procedures for membership in line with the new membership policy. The organizational changes will enable physician members to participate actively in the work of various sections of the council. The Committee's report will be presented at the next annual meeting of the Scientific Council in April, 1952.

ANNUAL MEETING RESERVATIONS

All those planning to attend the Association's Annual Meeting and Scientific Sessions at the Hotel Statler, Cleveland, April 18–20, 1952, should make room reservations with the *Housing Bureau*, Mr. Martin C. Dwyer, 511 Terminal Bldg., Cleveland, at the earliest possible date.

PROGRAM COMMITTEE

The full Program Committee for the Annual Scientific Sessions of the Association, to be held in Cleveland April 18 and 19, 1952, is as follows: Irvine H. Page, M.D., Chairman, Cleveland; Edgar V. Allen, M.D., Rochester, Minn.; Benjamin Baker, Jr., M.D., Baltimore; Paul B. Beeson, M.D., Atlanta; Robert A. Bruce, M.D., Seattle; Albert Dorfman, M.D., Chicago; Thomas J. Dry, M.D., Rochester, Minn.; G. Lyman Duff, M.D., Montreal; F. Lowell Dunn, M.D., Omaha; J. Russell Elkinton, M.D., Philadelphia; Thomas Findley, Jr., M.D., New Orleans; Arthur J. Geiger, M.D., New Haven; John W. Gofman, M.D., Berkeley, Calif.; Dwight E. Harken, M.D., Boston; Howard E. Heyer, M.D., Dallas; Charles E. Kossman, M.D., New York; Louis B. LaPlace, M.D., Philadelphia; Victor Lorber, M.D., Cleveland; Helen E. Martin, M.D., So. Pasadena, Calif.; Arthur J. Merrill, M.D., Atlanta; W. F. H. M. Mommaerts, M.D., Durham; Alan Moritz, M.D., Cleveland; George A. Perera, M.D., New York; Reno R. Porter, M.D., Richmond, Va.; Lowell A. Rantz, M.D., San Francisco; Francis F. Rosenbaum, M.D., Milwaukee; Francis F. Schwentker, M.D., Baltimore; James A. Shannon, M.D., Bethesda, Md.; Jeremiah Stamler, M.D., Chicago; Frederick J. Stare, M.D., Boston; Helen B. Taussig, M.D., Baltimore; George E. Wakerlin, M.D., Chicago; James V. Warren, M.D., Atlanta; Carl J. Wiggers, M.D., Cleveland.

Those wishing to present papers are reminded that an abstract in triplicate, not exceeding 300 words, should be sent before January 1, to Dr. Irvine H. Page, Cleveland Clinic, 2020 E. 93 Street, Cleveland 6, Ohio.

SECTION ON CIRCULATION

Hugh Montgomery, M.D., Philadelphia, has been chosen Chairman of the Section on Circulation of the Association's Scientific Council. Nelson Barker, M.D., Rochester, Minn., was named Vice-Chairman and Grace M. Roth, M.D., also of Rochester, was named Secretary-Treasurer.

"RECOMMENDATIONS FOR BLOOD PRESSURE DETERMINATIONS"

The Association's "Recommendations for Human Blood Pressure Determinations by Sphygmomanometers," printed simultaneously in the October issue of CIRCULATION and the October 13 issue of the Journal of the American Medical Association will be available in booklet form. Application should be made to the National Office, 1775 Broadway, New York 19, N. Y., or to affiliated heart associations.

HEART BULLETIN SUBSCRIPTIONS

Plans have recently been announced for sponsorship of subscriptions on a statewide basis to the projected bimonthly "Heart Bulletin," which is scheduled for publication starting early next year.

The price per annual subscription will be $1.56 including postage, when purchased by a local or state agency—an affiliated Heart Association, State Medical Society, or State Health Department—for most of the physicians in a state.

The "Heart Bulletin" will be published by the Medical Arts Publishing Foundation, a nonprofit public service institution in Houston, Texas. The magazine will be designed for physicians in general practice to stimulate their interest in cardiovascular-renal diseases. It will not duplicate any other publication of the AHA. An Advisory Board composed of specialists in the field will be selected in consultation with the American Heart Association and the U. S. Public Health Service.